Clinical Ophthalmology

A Guide to Diagnosis and Treatment

Marieta Dumitrache
Editor

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Preface

This book, *Clinical Ophthalmology: A Guide to Diagnosis and Treatment,* is written by a group of exceptional ophthalmologists, physicians within the academic and professional community.

This book presents, in a synthetic and up-to-date manner, the main elements of ophthalmological medical pathology.

The material is easily accessible, has a practical character, and follows an algorithm of medical information useful for clinical guidance; for each eye condition, there are descriptions of ocular and systemic signs and symptoms, risk factors, evolution, and clinical management.

The book serves as a reference for the practicing ophthalmologist, as a medical guide for diagnosis, and treatment of various ohptalmological medical conditions.

It deals with ophthalmological pathology, taking into account the anatomical structures of the eye, initial presenting symptoms for diseases of the eye appendages (orbit, eyelid, lacrimal apparatus, conjunctiva) and those of the eyeball (cornea, uvea, retina, optic nerve, cataract, glaucoma, retinal detachment, tumors).

The richly selected Table of Contents covers a wide variety of Ophtalmological pathologies.

The book is an up-to date theoretical and practical guide and describes classical medical-surgical therapeutic procedures, as well as current and emerging clinical advances in ophtalmology.

The material provides quick access to information, guides the positive and differential diagnosis; it describes appropriate therapeutic indications and techniques, disease specific and individualized to patient condition, in a personalized approach that takes in consideration clinical signs and laboratory values alike.

The contents make it possible to navigate this book easily.

This book is useful for ophthalmology trainees and practicing clinicians and focuses on reviews of clinical ocular pathology, current aspects of ophthalmology treatments, and new surgical techniques within this specialty.

Bucharest, Romania — Marieta Dumitrache

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About the Editor

Marieta Dumitrache, MD, PhD, is an accomplished academic ophthalmologist. Her academic career spans 50 years, during which she has authored more than 40 book chapters and over 60 scientific papers published or presented at national meetings.

Dr. Dumitrache has single handedly edited the only Comprehensive Ophtalmology Textbook in Romania; the material has underwent many editions in the last 30 years; many generations of Romanian ophthalmologists use this source for ophthalmology boards or in regular clinical practice. Additionally, she has edited more than 25 volumes on clinical ophthalmology, including the essential ophthalmology textbook currently used by trainees to pass their specialty boards. Professor Dumitrache work includes contributing books as author/editor at times focusing on topics covered less in the literature and by the publishing houses; some of those include topics such as pediatric ophthalmology and neuro-ophthalmology. Two of those unique works received highest academic recognition in Romania, Academy of Science Book Award (2011 for the work on Ocular Emergencies) and The Romanian Academy Award (2016 for the book on Ocular Emergencies).

Her scholarly activity also includes published papers in high impact journals in USA, UK, and India. Her research activity includes many collaborations with academic ophthalmologists within Romania and abroad; in her academic career, dr Dumitrache advised more that 20 PhD students on research projects that have been published in many ophtalmological journals, national and international alike.

Dr. Dumitrache served as the Chair of the Department of Ophthalmology from 1986 to 2011; she has made significant contributions to its growth by adding new faculty and clinical services. She had dedicated her clinical mission to improving patient outcomes by ensuring all patients have access to excellent and high standard clinical care. She is a talented surgeon with tens of thousands surgeries performed during her many years of activity; she has been a mentor to many generations of trainees, now highly accomplished ophthalmologists.

During her career as an academic ophthalmologist, Dr. Dumitrache essentially contributed to the advancement of the Ophthalmology Specialty in Romania and abroad, in a concerted tripartite mission that spans more than 50 years; she focused on clinical excellence to improve patients' outcomes, conducted state-of-the-art scholarly activity and research, and mentored and educated many generations of ophthalmologists.

In June 2024, Professor Marieta Dumitrache has been elected as honorary member of the Academy of Medical Sciences of Romania, in recognition of her excellent scientific and professional career.

Professor Marieta Dumitrache, MD, PhD

Book chapters Published in

- Advancement and new understanding in Medical Science, 2024, vol. 8, ISBN-978-81-970,671-7-4, Marieta Dumitrache, Teodora Adamescu—Etiopatogenic therapeutic strategies in Behcet's disease with ocular complication.
- Current progress in Medicine and Medical Research, 2023, vol.4, chapter 1, ISBN 978–81–19,315-85-7, Marieta Dumitrache, Miruna Cioboată, Alina Ciocâlteu, Rodica Lascu, M. Manea, capitol, The clinical therapeutic guidelines in pediatric glaucoma.
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Chapter 1
Congenital eye diseases

Marieta Dumitrache

Abstract **Congenital malformations** of the eye and the appendages of the eyeball are rare, and affect the anatomical structures of **the orbital walls** (cranial, craniofacial synostoses), **eyelids** (palpebral ptosis, palpebral coloboma, entropion, epicanthus), the **lacrimal apparatus** (lacrimal gland rarely, tear ducts with imperforation or atresia of the lacrimal puncta). Congenital anomalies of the **cornea** are anomalies of size and curvature (microcornea, megalocornea, flat cornea), and structural anomalies (iridocorneal dysgenesis associated with glaucoma). **Corneal dystrophies** are anterior, stromal, endothelial and ectatic (keratoconus, keratoglobus), corneal dystrophies. **Congenital anomalies** of the uvea are possible: coloboma, corectopia, pupillary membrane, pigmentation anomalies. **Congenital cataract** with partial or total opacification of the lens can be metabolic, present in chromosomal aberrations (trisomy 13, 15, 18, 21-Down), associated with the following syndromes: Lowe, Fabry, Hallerman-Streiff, Marfan. **Primitive congenital glaucoma** includes isolated trabeculodysgenesis - Buphthalmia (primitive early congenital glaucoma) and associated (aniridia, Petters, Acsenfeld, Rieger anomaly) and can also be present in syndromes, such as: Sturge Webber, Pierre - Robin, Bourneville, von Reclinhaussen. **Congenital anomalies of the vitreous** are developmental anomalies: pupillary membrane, persistent fetal vasculature. **Vitreoretinal dystrophies** (Norrie, Pigmenti incontinence, Goldman-Favre, juvenile retinoschisis). Congenital anomalies of the **optic disc** can be present through myelin fibers, papillary coloboma, morning glory, vascular anomalies of the papilla.

Keywords Craniofacial cranial synostoses · Palpebral ptosis · Coloboma · Entropion · Microcornea · Megalocornea · Iridocorneal dysgenesis · Pupillary membrane · Corneal dystrophies · Iris coloboma · Congenital cataract · Aniridia · Buphthalmia · Myelin fibers · Papillary coloboma

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Congenital Orbital, Craniofacial Malformations

Malformations Involving the Orbital Walls

Craniosynostosis

Scaphocephaly—premature suture of the sagittal suture; it is accompanied by the anteroposterior elongation of the skull, with prominent frontal bosses.

Brachycephaly—premature synostosis of the bicoronal suture; flattened skull, high forehead and frequent ophthalmological abnormalities, exophthalmos, hypertelorism, strabismus, small orbits.

Trigonocephaly—premature suture of the metopic suture; triangular skull with aplasia of frontal bosses, close-set eyes, hypotelorism.

Plagiocephaly—premature suture of the unilateral coronary suture

- produces asymmetric deformation of the skull.

Oxycephaly—early suture of multiple cranial sutures with small oval skull, flat forehead, associated with neuro-ophthalmological complications.

CRANIOFACIAL SYNOSTOSIS–can produce neurological disorders: progressive intracranial hypertension, epilepsy and ophthalmological disorders with exophthalmos, hypertelorism, oculomotor disorders, decreased visual acuity (VA) [1–3].

Crouzon Syndrome

- synostosis of the coronal, sagittal, lambdoid (rarely) sutures, deformed skull
- frontal hypoplasia, sphenoid, ethmoid, jaw
- exophthalmia, hypertelorism, V syndrome
- intracranial hypertension with papilledema, optic atrophy
- Mental retardation

Acrocephalosyndactyly—Crouzon's disease plus hand, foot syndactyly, with hypertelorism and exophthalmos in a reduced manner.

Goldenhar syndrome—oculo-auriculo-vertebral dysplasia, sometimes associated with Down syndrome.

Waardenburg syndrome—inner canthus dysplasia, eyebrows confluence, iris heterochromia, hyperpigmentation of the fundus.

Hallermann-Streiff syndrome—mandibular hypoplasia and pointed nose, associated with congenital cataracts and glaucoma.

Pierre Robin syndrome—micrognathia, glasoptosis, palatoschisis associated with strong myopia, congenital glaucoma, retinal detachment.

FACIAL CLEFT SYNDROMES—associated with microphthalmia, upper and lower eyelid coloboma.

HYPERTELORISM—increase in the interorbital distance (more than 30 mm in an adult).

Malformations Involving the Orbital Contents

- **congenital anophthalmia** is the absence of the eyeball through the absence of the primary vesicle or early destruction;
- **microphthalmia** has varied clinical aspects with eyeball present but small; it can be complicated by ocular abnormalities (corneal dystrophy, cataracts, pupillary membrane, primitive vitreous, retinal dysplasia) and/or visceral abnormalities.

Malformations Affecting the Dimensions of the Eyeballs

- ***Keratoglobus***—enlargement of the structures of the eyeball

Buphthalmos—enlargement of the eyeball and cornea due to increased IOP
Nanophthalmos—small eye with normal structure
Microphthalmia—small eye with abnormal structures.

Congenital Diseases of the Eyelids [3–5]

- Uni-, bilateral congenital palpebral ptosis
  - alone or associated with: SR paralysis, SR hypofunction, inferior oblique, epicanthus, blepharophimosis, myopic astigmatism
  - the lifting and lowering of the eyelid is done with difficulty
  - although vision is normal, amblyopia may occur.
- **Marcus Gunn synkinesis**—paradoxical eyelid movement (lifting of the eyelid during sucking)
  - synkinetic movements may or may not be associated with palpebral ptosis
- **Eyelid coloboma**—in the upper eyelid, it is located in the triangular middle third with the base at the edge of the eyelid with exposure anomalies; in the lower eyelid, the coloboma is located laterally (Franceschetti syndrome, Treacher Collins syndrome)
  - It can be associated with microphthalmia, iris coloboma
- Ankyloblepharon
  - lateral localization, 1 → 4–5 integument bands joining the eyelids
- **Distichiasis**—supernumerary presence of cilia behind the normal row of cilia
- **Entropion**—rarely; it can be associated with epicanthus
- **Ectropion**—very rarely, it is isolated or associated with blepharophimosis, telecanthus, epicanthus, ptosis
- The telecanthus
  - lateral displacement of the medial commissure
  - may be associated with epicanthus (Waardenburg syndrome)
  - asymptomatic
- **Epicanthus**

  - vertical tegumentary fold in the medial portion of the palpebral fissure, bilaterally, symmetrical
  - racial sign (Asians) or may be present in Down syndrome
  - asymptomatic, but if it is extended, it can give convergent pseudostrabismus
  - it may be associated with ptosis.

- Blepharophimosis
  - reduction of the palpebral fissure, bilateral, symmetrical
  - associated with telecanthus, ptosis, inverse epicanthus

- Skin anomalies
  - Blepharochalas is due to atrophy of the dermis and loose skin
  - Epiblepharon with horizontal skin fold parallel to the palpebral margin + entropion of the lower eyelid

- **Ablepharia–**complete absence of the eyelid, very rarely
- **Microblepharia—**very rare, small eyelids (vertical + lagophthalmos).

The Tear System

- **Congenital disorders of the lacrimal gland** [6]
  - Lacrimal gland agenesis - rare
  - ***Riley-Day syndrome*** - familial dysautonomia

Ocularly
- hypo-, alacrimia
- reduction of blinking
- epithelial corneal dystrophy
- dark brown eyelids

Generally
- hypersalivation, hypersweating
- reduced life expectancy
- ***"Crocodile tears" syndrome*** - lacrimation to stimuli, which triggers salivation; It is present in Moebius, Stilling-Duane syndrome.
- ***Ectopia of the lacrimal gland*** which can be located in the orbit, subconjunctivally.
  - **Congenital disorders of the tear ducts**

- ***Imperforation or atresia of the lacrimal puncta*** may be asymptomatic if only the upper puncta is involved, otherwise hyperlacrimation occurs;
- ***Canalicular agenesis*** with or without lacrimal puncta atresia is accompanied by epiphora;

- ***Point or bifid canalicule (more often inferior)***—they can open into the sac, one, the other, subconjunctivally;
- ***Supernumerary points***—frequently asymptomatic + blepharophimosis;
- ***Congenital lacrimal duct fistula*** (rarely), may be asymptomatic or accompanied by lacrimation, mucoid secretion + other lacrimal and/or general abnormalities; preauricular, tracheobronchial fistula;
- ***Congenital lacrimal sac fistula*** in which the lacrimal sac opens to the skin below the internal palpebral ligament; can be asymptomatic + other anomalies;
- ***Lacrimal diverticulum*** (on the duct or sac)
  - sac diverticulum shows lacrimation without nasolacrimal imperforation, tumor in the inner canthus that evacuates upon compressions; instrumental exploration is normal (differential diagnosis with mucocele).
- Congenital lacrimal-nasal imperforation
  - lacrimal-nasal impermeability is suspected by the family in a newborn with: chronic lacrimation, tears that can run down the cheek + chronic conjunctivitis aggravated by nasopharyngeal superinfection;
  - lacrimal-nasal obstruction (uni-, bilateral) is evidenced by continuous lacrimation, initially clean, tears that can become superinfected, causing congenital dacryocystitis;
  - lacrimal-nasal obstruction requires conservative treatment (massage of the lacrimal sac, local hygiene, antibiotic eye drops—netilmicin, ciprofloxacin, moxifloxacin) and/or instrumental—diagnostic and therapeutic survey at a young age, 3–7 months old. Nasal intubation with silicone tubing is possible.
- Acute dacryocystitis (rare) is an abscess of the sac distended by the accumulation of tears and their superinfection: it requires survey (with great care), incision and drainage, antibiotics.
- Lacrimal sac mucocele
- ***Syndromes associated with tear duct abnormalities*** [7]
- *Treacher Collins Syndrome*
  - Lacrimal puncta anomalies;
  - eye abnormalities—telecanthus, microphthalmia, palpebral coloboma
  - systemically: hypoplasia of the median part of the face, maxillary, zygomatic
  - deafness
- *Apert syndrome*
  - dysgenesis punctum, canaliculi, lacrimal-nasal canal
  - hypertelorism
  - facial hypoplasia (median)
  - Syndactyly
- Orbito-maxillary cleft syndrome—Moran I
  - canalicular dysgenesis, lacrimal-nasal duct

  - dermolipomas, sclerocorneal
  - hypoplasia of the wing of the nose, lip, cheek
  - eyebrow malformations

- Moran II syndrome

  - sac, lacrimal-nasal canalanomalies
  - corneal ulcer
  - coloboma of the iris
  - facial atrophy
  - upper lip cracks

Congenital Corneal Anomalies [8, 9]

Size and Curvature Anomalies

The Microcorneea

- flat cornea with corneal diameter less than 10 mm, normal thickness. Small anterior chamber; induces high hypermetropia, angle-closure glaucoma (20%);
- eye diseases:

  - congenital cataract
  - persistence of primitive vitreous, coloboma
  - ON hypoplasia
  - microphthalmia (small, abnormal eye)
  - nanophthalmia (small eye, normal)

- systemic diseases—Ehlers-Danlos syndrome, achondroplasia, myotonic dystrophy.

Megalocornea

- corneas greater than 12 mm in diameter, of normal thickness, bilaterally, more common in men
- eye diseases:

  - congenital cataract, microcornea
  - crystalline subluxation

- systemic diseases—Marfan syndrome, Down syndrome, Alport syndrome.

Flat Cornea

- flattened corneal curvature, keratometry 20–30 D;
- small anterior chamber with possible abnormalities that can cause angle-closure glaucoma;
- eye conditions;

  - microcornea

- sclerocornea
- congenital cataract
- coloboma of the iris
- angle closure, open angle glaucoma

Anomalies of the Structure

- Iridocorneal dysgenesis, anterior segment cleft syndrome, bilateral, asymmetric, associated with glaucoma

Posterior Embryotoxon
- anterior displacement of the Schwalbe ring thickened with peripheral iris adhesion - 10% of population
- asymptomatic for a long time, it can be complicated with ocular hypertension
- associated with aniridia, ichthyosis.

Axenfeld Anomaly
- posterior embryotoxon with peripheral iris tissue clamps
- rarely associated with glaucoma (juvenile more common)

***Riegeranomaly* [10]**
- posterior embryotoxon
- hypoplasia of the iris stroma
- correctopia, polycoria
- uveal ectropion
- cataract
- RD
- ON hypoplasia
- macular degeneration
- leukoma

***Rieger Syndrome*—Rieger Anomaly Associated With [10]**
- dental anomalies—absent or small upper incisors
- facial anomalies: hypoplasia of the lower jaw, aplasia of the base of the nose, hypertelorism
- bone abnormalities
- cardiac abnormalities
- umbilical hernia
- pituitary insufficiency

***Peters Anomaly*—Neural Crest Cell Migration Defect Between the 5th—8th Fetal Week [11]**
- central corneal opacity with adhesion to iris tissue, cornea with clear periphery, normal dimensions
- contact between lens and cornea in severe cases

- absence of central Descemet's membrane
- ocular comorbidities
  - glaucoma 50%
  - anterior polar cataract
  - sometimes microphthalmia, microcornea, sclerocornea, Axenfeld anomaly
- systemically: pulmonary hypoplasia, congenital heart disease

Aniridia—abnormality of neuroectodermal development

- onset at birth with nystagmus, photophobia
- ocular comorbidities:
  - subtotal absence of iris that is reduced to a collarette
  - hypoplasia of the papilla and fovea
  - peripheral corneal opacities
  - glaucoma in 50–75% of cases, difficult to treat, with early goniotomy, drainage implants, cyclodestruction
  - lens subluxation
  - partial, total congenital cataract
- clinical diversity
  - AN I—60% without systemic changes
  - AN 2—Miller syndrome—33% can develop Wilms's tumor before the age of 30
  - AN 3—Gillespie syndrome with mental retardation and cerebellar ataxia
- Posterior keratoconus
  - Posterior corneal depression
- Sclerocorneea
  - opaque peripheral cornea with scleral appearance
  - bilateral, asymmetric
  - ocular damages: flat cornea, microphthalmia, Wachendorf membrane

Corneal Dystrophies

Anterior Corneal Dystrophies **[4, 12]**

- Microcystic dystrophy—Cogan
- epithelial microcystic punctate opacities, isolated or associated subepithelial map-dot-lesions
- onset: 10–20 years old, 10% of patients may have recurrent corneal erosions towards the age of 30 years (painful)
- Meesmann dystrophy

  - small intraepithelial cysts, concentrated in the center of the cornea, with irregular thickening of the epithelium
  - asymptomatic in children

- Reis—Bücklers dystrophy
  - Bowman's membrane dystrophy, symmetrical, with round, fine, centrally located, subepithelial white/gray opacities
  - onset during childhood with recurrent corneal erosions.

Corneal Stromal Dystrophies **[4]**

- Schnyder corneal dystrophy
- bilateral with onset in the first years, asymptomatic
- central stromal corneal opacity (white-yellow) with well-circumscribed margins (cholesterol deposits) requiring excimer laser photokeratectomy, corneal grafting
- Lattice corneal dystrophy type I—Biber Haab Dimer
  - recurrent corneal erosions towards the age of 10
  - linear opacities that may be masked by a diffuse corneal opacification (amyloid deposits)
- Lattice corneal dystrophy type II– Meretoja syndrome
  - middle age, VII palsy and corneal touch
  - finer and radiating short linear opacities (type 1 difference) (amyloid deposits)
  - systemic associations: progressive peripheral and cephalic neuropathy, dysarthria, dry, lax skin, protruding lips, drooping ears, amyloidosis of the heart and kidney
- Lattice corneal dystrophy type 3A
  - onset around the age of 60 with VA decrease through thick linear corneal opacities
  - require keratoplasty
- Granular dystrophy—Groenow I
  - onset around the age of 10 with recurrent corneal erosions
  - small, well-demarcated granular whitish anterior stromal opacities (amorphous hyaline deposits) that may converge
  - slow evolution, requires a corneal graft
- Avellino dystrophy
  - onset around the age of 20, with recurrent erosions
  - granular opacities in the superficial stroma associated with deep linear opacities, evoking a lattice dystrophy (hyaline and amyloid deposits)
- Macular dystrophy—Groenow II
  - onset around the age of 10, with progressive VA decrease (rare, severe), recurrent corneal erosions

  - poorly demarcated dense gray opacities that give a cloudy appearance to the corneal stroma: evolve towards Descemet membrane and to periphery
  - opacities contain abnormal aggregates of glycosaminoglycans (mucopolysaccharides) that may recur after keratoplasty

- Gelatinous dystrophy (familial amyloidosis)

  - onset in the first 20 years with severe photophobia, lacrimation, decreased VA through recurrent erosions
  - confluent gray nodules with a berry appearance (initially, the nodules are separated by clear areas), located centrally, develop deeply and peripherally
  - amyloid deposits under the epithelium and in the anterior stroma.

Corneal Endothelial Dystrophies **[4, 12]**

- Fuchs endothelial dystrophy
- bilateral, asymmetric, progressive, with onset in patients after the age of 60, more frequent in women
- is the most common endothelial corneal dystrophy in which the cornea guttata progresses to corneal edema and subepithelial fibrosis
- ***corneea gutaata—***are protrusions (guttae) at the level of Descemet membrane, visible under backlight, which tend to merge and are associated with a fine pigmentation of the endothelium
- central stromal edema and bullous keratopathy; when the thickness of the central cornea is greater than 1000 microns, epithelial edema occurs that produces microcysts, which merge, break or give painful episodes upon awakening
- subepithelial fibrosis—occurs after recurrent episodes of bubble rupture;
- ocular associations: bullous keratopathy, primary open angle glaucoma, axial hypermetropia;
- treatment: antiedema eye drops, artificial tears, timolol, contact lenses, corneal graft, amniotic membrane graft.
- Posterior polymorphic dystrophy

  - present at birth with very fine vesicular, linear and geographic endothelial abnormalities that may progress to corneal edema;
  - associations with: irido-corneo-endothelial syndrome, Alport syndrome.

- Congenital hereditary endothelial dystrophy—is the most common congenital dystrophy and is manifested by bilateral corneal edema

  - endothelial dystrophy given by the focal or diffuse absence of the corneal endothelium, with marked corneal thickening;
  - there are two forms: with more severe non-progressive AR transmission and associated with corneal edema from birth and (severe) nystagmus and with milder, progressive AD transmission without nystagmus;
  - requires perforating keratoplasty

Corneal Ectatic Dystrophies

- Keratoconus

- onset at puberty with decrease in VA through myopia and astigmatism, myopia with evolution towards irregular astigmatism;
- clinically, it is a paracentral, bilateral, non-inflammatory corneal ectasia with progressive corneal thinning resulting in a central, paracentral conical protrusion of the cornea;
- initial signs [13];
- Rizzuti sign—cone-shaped reflection of the nasal cornea;
- Vogt's sign—fine vertical oblique stromal striae, parallel to the most curved meridian;
- irregular mires on keratometry
- pulsatile mires on applanation
- corneal topography
- late:
- Manson's sign—is the protrusion produced by the cornea on the edge of the lower eyelid when looking down
- central, paracentral stromal thinning with apical protrusion
- Fleischer ring—located at the base of the cone

Complications [13, 14]

- acute corneal hydrops which is a significant corneal edema produced by Descemet membrane rupture and appears as a white disc-like opacity; does not lead to perforation unless there is trauma or excess corticosteroids have been used;
- ocular associations: blue sclera, aniridia, lens ectopy, vernal keratoconjunctivitis, pigmentary retinopathy, Leber congenital amaurosis;
- systemic associations: trisomy 21, Turner, Ehlers—Danlos, Marfan, osteogenesis imperfecta, mitral valve prolapse;

Treatment [14]

- avoiding trauma (rubbing the eyes);
- optical correction
- rigid contact lenses for astigmatism
- intracorneal rings
- keratoplasty for advanced keratoconus.
- Keratoglobus
  - is a non-progressive ectatic dystrophy with a completely thin cornea and prominent as a globular sphere with increased corneal diameter and descemetic folds;
  - systemic associations—Leber congenital amaurosis, blue sclera;
  - protection against eye injuries is very important;
  - if necessary, scleral lenses, keratoplasty (modest results).
- Marginal pellucid degeneration
  - ectatic corneal dystrophy with peripheral noninflammatory, bilateral, painless corneal thinning;
  - onset at 30–50 years old, with evolutionary astigmatism;

– corneal thinning of 1–2 mm and 4–6 mm long, inferior, in the band between 4 and 8 o'clock, with the protrusion of the overlying central cornea; it is separated from the limbus by an area of clear cornea;
– very rarely, Descemet rupture can be complicated with acute hydrops.

Treatment
- initial optical correction with air, contact lenses;
- surgical treatment (technically difficult and limited success), cuneiform resections, large diameter cornea graft, peripheral lamellar keratoplasty.

Congenital Anomalies of the Sclera

Abnormalities of Organogenesis [5, 8]

Microphthalmia
- It is a smaller-than-normal size globe and may be isolated or associated with other abnormalities.
- It is produced by developmental defects (associated with colobomas of the iris, ciliary body, choroid, ON head) or intrauterine fetal infections (in rubella).

Nanophthalmia
- It is a microphthalmic but normal eye, bilateral AD or AR, with hypermetropia of high values (up to 20D) and uniformly thickened sclera (up to 2 mm).
- It can be complicated by: late-onset angle-closure glaucoma, uveal effusion (through thickening of the sclera) associated with non-rhegmatogenous RD.

Corneal and/or scleral coloboma—very rare.

Pigmentation Abnormalities of the Sclera

- ***Ocular melanosis*** (benign) with increased uveal pigmentation and abnormal scleral or episcleral pigmentation (slate gray)
- ***Nevus oto*** - pigmentation in the territory of the ophthalmic and maxillary branch of the Vth cranial nerve

Abnormalities of the Thickness of the Sclera

Congenital staphyloma is scleral ectasia located at the level of a thinned sclera

- *Posterior staphyloma in strong myopia*—with thin sclera in progressive myopia more pronounced in the posterior temporal area and around the optic disc.
- *Posterior congenital staphyloma* in patients without myopia and is frequently associated with microphthalmia
- *Congenital Ammon protrusion* is a posterior staphyloma with thin ectatic sclera and aplastic retina (with absence of RPE and choroid) can be complicated with macular tear and RD.

Congenital Affections of The UVEA [8, 9]

- Iridocorneal dysgenesis (see Cornea, Glaucoma)
  - posterior embryotoxon
  - Axenfeld anomaly
  - Rieger anomaly
  - Peters anomaly
- Coloboma
  - the absence of a portion of the uvea located predominantly inferonasally, produced by the incomplete closure of the embryonic fissure;
  - there is iris coloboma + other colobomas: coloboma of the ciliary body, choroid, lens, retina, optic nerve (ON), frequently bilateral with or without VA damage;
  - coloboma can be isolated or present in general syndromes: trisomy 13, 18, 22, Klinefelter, Turner, Goldenhar, Meckel, Aicardi, Lenz, Charge (Pagon) syndrome.
  - iris coloboma ± other colobomas: ciliary body, choroid, lens, retina, ON, frequently bilateral with or without VA damage;
- Lisch nodules
  - They can appear around the age of 5 and are present in neurofibromatosis type I (75%) in the form of small pigmented nodules, in contrast to the atrophy of the anterior iris.
- Brushfield spots
  - Circular spots around the pupil in the middle portion of the iris, present in Down syndrome, but also in normal individuals.
- **Congenital iris cyst -** can be located in the stroma or in the pigment epithelium.
  - do not treat if it does not affect VA;
  - the stromal cyst may recur after photocoagulation.
- Pupillary membrane

  - represents the incomplete involution of the fetal vascular tunic; is the most common congenital ocular anomaly and is present in 80% of dark-colored eyes and 35% of light-colored eyes;
  - represents iris traveae attached or not to the pupil, which can float freely in the pupil or attached to the surface of the lens and may be associated/or not with previous polar cataract;
  - rarely affects VA.

- Congenital irian ectropion
  - present in neurofibromatosis, may be associated with uveal ectropion of the pigment epithelium;
  - the congenital iris form can be accompanied by: high iris insertion, angle dysgenesis + glaucoma.

- Microcoria
  - small, eccentric, unilateral pupil;
  - it can be associated with iris coloboma;
  - can cause amblyopia.

- Corectopia
  - is the displacement of the pupil;
  - can be present in: Axefeld syndrome, Rieger syndrome, irido-corneo-endothelial syndrome.

- Dyscoria
  - abnormally shaped pupil;
  - can be isolated or associated with: Axenfeld syndrome, Rieger syndrome, lens ectopy, posterior synechiae.

- Pigmentation abnormalities
  - Increased pigmentation

    iris melanosis without pathological significance, with diffuse iris hyper-pigmentation but normal melanocytes
    oculocutaneous melanocytosis

  - Decreased pigmentation

    congenital Claude Bernard-Horner syndrome with discolored iris on the side affected by sympathetic paralysis;
    Waardenburg syndrome—associates iris heterochromia with inner canthus dystopia, thick eyebrows, deafness.

  - Heterochromia iridium

    different coloration between the iris of the two eyes;

it can be produced by increased pigmentation or decreased pigmentation in one eye.

Congenital Cataract

- Congenital cataract is a disorder of the transparency of the crystalline lens, with its partial or total opacification.
- Crystalline opacities may be associated with:
  - anterior segment lesions:

    keratopathy
    microphthalmia
    glaucoma
    persistence of primitive vitreous

  - lesions of the posterior segment

    chorioretinitis
    Leber's amaurosis
    rubella retinopathy
    hypoplasia of the fovea, optic nerve

  - signs of amblyopia

    absence of central fixation
    nystagmus
    strabismus

- Shape abnormalities of the lens [3, 12]
- *Microspherophakia*
  - lens small (in diameter) and spherical, which can change its position by falling into anterior chamber, pupil, with the production of pupillary block with closed-angle glaucoma;
  - etiologically:

    family - AD
    Marfan syndrome
    Weill-Marchesani syndrome
    hyperlysinemia
    congenital rubella
    isolated microspherophakia in Lowe, Alport syndrome

  - complications:

    crystalline myopia
    lens subluxation

- Lenticonus, lentiglobus
  - the lens capsule is thinned and the curvature of the lens is abnormal;
  - lenticonus is the conical protrusion and lentiglobus is the spherical protrusion;
  - the lenticonos may be anterior in Alport syndrome and/or posterior.
- Crystalline coloboma
  - it is the equatorial (inferior) sectoral agenesis with the absence of zonular fibers.

Metabolic Cataract [15]

Galactosemia—due to the absence of an enzyme that transforms galactose into glucose;

- at ocular level:
  - central crystalline opacity with "oil drop" appearance
- systemically:
  - vomiting, diarrhea
  - hepatomegaly
  - malnutrition
  - mental retardation
- Galactokinase deficiency
  - at ocular level: lamellar lens opacities
- ***Mannosidosis—***enzyme deficiency that causes the accumulation in tissues of oligosaccharides rich in mannose
  - systemically:

    short stature
    somatic changes
    mental retardation
- ***Hypoglycemia***
- ***Diabetes***
  - ocularly—rapidly progressive "snowball cataracts" in young diabetics.
- ***Hypocalcemia***
  - ocularly—anterior, posterior subcapsular crystalline opacities.
- ***Wilson's* disease**– hepatolenticular degeneration
  - produced by decreasing ceruloplasmin;

  - ocularly:

    Kayser Fleischer ring at Descemet level;
    "sunflower" cataract with ovoid copper oxide deposits in the anterior capsule;

- systemically:
  - liver cirrhosis
  - muscle stiffness (swallowing, chewing difficulty);
  - neurological signs

Congenital Cataract in Chromosomal Aberrations [7]

- Down syndrome TRISOMY 21
  - more common in children born by mothers over 35 years old
  - ocularly:

    epicanthic fold, hypertelorism
    keratoconus
    Brushfield spots, iris hypoplasia
    myopia
    congenital cataract

  - systemically:

    growth retardation, mental
    skeletal abnormalities
    aggressivity

- Trisomy 13, 15, Patau's syndrome
  - ocularly:

    microphthalmia, hypertelorism
    coloboma of the iris, optic nerve
    congenital cataract

  - systemically:

    microcephaly
    cardiac, CNS, renal malformations

- Trisomy 18
  - Mother over 40 years old
  - ocularly:

    ptosis, epicanthic fold

congenital glaucoma
corneal, crystalline opacities
optic atrophy

– systemically:

facial malformations
cardiac abnormalities
Meckel's diverticulum

- ***Turner syndrome***—gonadal dysgenesis
  - ocularly:

    exophthalmia, hypertelorism, ptosis, epicanthus
    keratoconus
    blue sclera
    cataract
    retinal hypopigmentation

  - systemically:

    mental retardation, growth restriction
    deafness
    cardiac and renal abnormalities

- ***"Cri du chat" syndrome***
  - ocularly:

    cataract
    strabismus

  - systemically:

    microcephaly
    growth retardation, mental
    cat's cry

General Syndromes Associated with Congenital Cataract [7]

- ***Lowe syndrome***—oculo-cerebro-renal syndrome
  - deficiency in amino acid metabolism, ARX, more common in boys;
  - ocularly—cataract with cortical opacities associated with:

    microspherophakia
    posterior lentiglobus
    glaucoma 50%

– systemically:

renal dwarfism, aminoaciduria
muscle hypotonia
osteomalacia
mental handicap

- ***Fabry (Krabbe)* disease–** diffuse angiokeratoma
  - Sphingolipidosis
  - ocularly:

    cornea verticillata
    crystalline opacities (25%)
    conjunctival, retinal telangiectasias
    paralysis III
    nystagmus

  - systemically:

    kidney failure (possible cause of death)
    diffuse angiokeratoma
    lung disease, cardiomyopathy
    peripheral neuropathies
    cutaneous telangiectasias

- ***Hallermann—Streiff syndrome–*** Mandibulo-oculo-facial dyscephaly syndrome
- Ocularly

  severe bilateral microphthalmia
  congenital cataract (possible spontaneous resorption or phacoantigenic uveitis)
  blue sclera
  papillary coloboma
  optic atrophy
  nystagmus
  strabismus

- systemically

  skull, face, mandible malformations, with mandibular hypoplasia, small pointed nose, bird-like facies, dental anomalies
  mental, postural retardation

- ***Myotonic dystrophy***
- creatine kinase disorders in skeletal muscle
- ocularly:

  ptosis
  anterior, posterior subcapsular cataract colored with crystals
  abnormal irregular movements

proliferative retinopathy (PR)

- ***Alport syndrome***
- IV collagen enzyme defect
- triad: anterior lenticonus, deafness, hemorrhagic nephropathy with renal failure
- ocularly:

  conjunctival concretions
  posterior corneal dystrophy
  anterior lenticonos
  spherophakia
  anterior polar congenital cataract
  optic disc drusen

- ***Niemann—Pick*** syndrome essential lipoid histiocytosis
- sphingolipidosis with lipid deposition in outer retinal layer due to enzyme deficiency
- ocularly:

  anterior, posterior subcapsular crystalline opacities
  cherry red macula
  optic atresia
  nystagmus

- ***Stickler syndrome***—progressive arthro-ophthalmopathy
- Type II collagen disorders
- ocularly:

  high, non-progressive myopia (8D) accompanied by vitreous changes and RD
  nuclear cataract, cortical opacities
  perivascular pigmentation

- systemically:

  arthropathy (can simulate juvenile arthritis)
  deafness
  short stature, facial hypoplasia, micrognathia, flattened nose, glossoptosis

- Congenital cataract in intrauterine infections

  toxoplasmosis
  rubella
  cytomegalovirus
  herpes simplex

- Hereditary ectopia lentis
- ***Familial ectopia lentis—***AD, symmetrical bilateral superotemporal subluxation of the lens
- ***Ectopia lentis et pupillae***

  AR

Bilateral ectopia lentis and pupillae in opposite directions

- ***Marfan syndrome***– congenital mesodermal dystrophy
- hereditary condition AD, generated by disorders in collagen synthesis (fibrillin anomaly) with skeletal, cardiac, ocular findings
- ocularly:

  bilateral symmetrical frequently superotemporal ectopia lentis with intact zonule
  myopia

    increase in the incidence of RD
    secondary glaucoma due to lens dislocation
    microspherophakia (small and spherical crystalline) more common in Weill—Marchesani syndrome
    uveal, macular, ON coloboma

- systemically:

  high thin waist, long arms and fingers, arachnodactyly
  joint hyperextensibility
  cardiovascular anomalies

- ***Weill—Marchesani syndrome***

  – Hyperplastic congenital mesodermal dystrophy,
  – AR, AD
  – ocularly:

    microcornea
    lenticular myopia
    microspherophakia with small spherical lens
    bilateral and inferior ectopia lentis
    secondary glaucoma due to dislocation of the crystalline lens
    optic atrophy

  – systemically:

    brachymorphy with short waist, short thick neck, broad chest, brachydactyly
    decreased joint flexibility
    hearing loss

- ***Homocystinuria***—recessive hereditary disease with disturbances in the metabolism of amino acids through abnormalities in the metabolism of methionine and its transformation into cysteine; enzyme deficiency produces cysteine accumulation in urine and blood;

  – ocularly—ectopia lentis with inferonasal lens subluxation (15% around 15 years old)
  – systemically:

increased incidence of thromboembolism
low methionine diet required
cysteine and B_6 supplements.

Other (Occasional) Causes of Ectopia Lentis
- aniridia
- Stickler syndrome
- Ehlers-Danlos syndrome
- hyperlysinemia

Ectopia Lentis Complications
- refractive errors caused by crystalline myopia or hypermetropia due to significant dislocation
- cataract
- endothelial decompensation
- phacoantigenic uveitis

Treatment
- optical—for the correction of astigmatism or aphakia
- surgical—in glaucoma, cataract

Primary Congenital Glaucoma [3, 4, 12]

Early
- **Isolated trabeculodysgenesis—*Buphthalmia* (early primary congenital glaucoma)**
- stoppage in the development of the iridocorneal angle during the intrauterine stage of 6 months, and is accompanied at birth by dysmorphic, dysgenic development of the iridocorneal angle (trabeculodysgenesis) with the absence of the angle and the concave or flat insertion of the iris directly on the trabeculae:
- bilateral (75%) asymmetrical, more common in boys:
- sporadic (90%), AR through the GLC3A in 2p21 and GLC3B in 1p36 genes;
- clinical forms:
- true congenital glaucoma −40% with high intrauterine IOP;
- childhood glaucoma with onset before the age of 3;
- juvenile glaucoma - onset between 3 and 16 years old
- symptoms:
- lacrimation
- photophobia
- blepharospasm
- clinical signs:
- buphthalmia (enlarged eye), if IOP is increased before the age of 3
- horizontal corneal diameter greater than 13 mm
- corneal edema

- descemetic tears - Haab striae
- papillary excavation that may regress if IOP normalizes
- clinical evaluation by eye examination under general anesthesia with eye fundus examination, gonioscopy, IOP measurement and corneal diameters;
- Treatment:
- surgical (election therapy); goniotomy when the angle is visible;
- trabeculectomy when the cornea is opaque, or in case of failure of goniotomy (multiple);
- trabeculectomy can be effective especially if combined with trabeculotomy and antimetabolites.
- **Associated trabeculodysgenesis**
  - ***Corneo-trabecular dysgenesis-Posterior embryotoxon***
  - ***Irido-corneo-trabecular dysgenesis***
- ***Aniridia—***is an abnormality of neuroectodermal development secondary to a genetic mutation that consists in the subtotal absence of the iris (there is always an iris rudiment at the root)
  - onset at birth, bilateral, with nystagmus and photophobia;
  - can be associated with: epibulbar dermoid, glaucoma (50–75%), difficult to treat, cataract, ectopia lentis fovea and papilla hypoplasia.
- ***Congenital ectropion of the retinal pigment epithelium***
  - unilateral, rare
  - juvenile congenital glaucoma (before the age of 3)
  - can be associated with: Axenfeld, Rieger, Recklinghausen syndromes.
  - ***Irido-corneo-trabecular-dysgenesis***
- ***Central***
  - ***Peters anomaly***
- sporadic inheritance, rarely RA, bilateral;
- clinical signs:
  - central corneal opacity with iris tissue adhesions associated with stromal and Descemet membrane defects
  - the periphery of the cornea is clear
  - glaucoma (50%), frequently congenital
  - anterior polar cataract
- ***Peripheral***—iridocorneal dysgenesis
  - ***Axenfeld anomaly***

    at gonioscopy - posterior embryotoxon with peripheral iris tissue bands glaucoma, rarely
  - ***Rieger anomaly***

posterior embryotoxon
hypoplasia of the *iris stroma*
corectopia
uveal ectropion

- ***Rieger syndrome***
  - ***Rieger anomaly associated with***:

    dental anomalies—small teeth
    facial anomalies—maxillary hypoplasia, telecanthus, hypertelorism
    umbilical hernia

- Glaucoma associated with systemic diseases [7, 9]

Sturge—Weber Syndrome
- The iridocorneal angle has a common origin in the neural crest with the facial bones, teeth, cartilage, and meninges; because of this, congenital glaucoma can be associated with general and ocular malformations;
- cutaneous hemangioma in the territory of the trigeminal nerve—*nevus flamens* ± facial hemiatrophy, leptomeningeal, choroidal, episcleral hemangioma;
- glaucoma in 50% of cases by trabeculodysgenesis or increased episcleral venous pressure.

Neurofibromatosis I—von Recklinghausen's Disease
- AD, with irregular penetrance and variable expressivity
- cutaneous, visceral, CNS, peripheral NS neurofibromas, absence of the greater wing of the sphenoid;
- ocularly:
  - unilateral glaucoma (sometimes present at birth or immediately after);
  - glaucoma is caused by: anomalies of the angle, associated with congenital ectropion of the uvea, obstruction of the angle by neurofibromatous tissue, synechiae, or fibromatous thickening of the ciliary body;
  - glaucoma can be associated (frequently, 50%) with plexiform neurofibroma on the ipsilateral upper eyelid;
  - Lisch nodules, glioma, optic nerve sheath meningioma

Lowe Syndrome
- present in males (females have punctate crystalline opacities)
- ocular anomalies: congenital cataract, infantile glaucoma, strabismus, nystagmus, miosis;
- systemically:
  - renal abnormalities (aminoaciduria)
  - mental retardation

Pierre Robin Syndrome
- ocularly:
- congenital glaucoma

- coloboma of the uvea
- strong myopia
- RD
- systemically:
  - cleft palate
  - micrognathia
  - mandibular hypoplasia
  - glossoptosis

Bourneville Tuberous Sclerosis—Rare Phakomatosis, AD, Sporadically

- ocularly:
- ON or retinal astrocytoma;
- corneal opacities;
- pigmented spots on the iris;
- crystalline opacities;
- glaucoma
- systemically:
  - coutaneously 90%:

    facial angiofibroma (butterfly wings sebaceous adenoma of the cheek)
    "cafe-au-lait" spots
  - at cerebral level:

    cerebral astrocytoma
    epilepsy
    mental handicap
  - viscerally: renal, cardiac, pulmonary affections, spina bifida;

Nevus of Ota

- ocularly:
- episcleral pigmentation
- iris hyperchromia
- choroidal hyperpigmentation
- glaucoma
- melanoma, uvea, orbit, ON

Rubinstein—Taybi syndrome

- ocularly:
- hypertelorism, epicanthic fold, antimongoloid slant
- ptosis, long cilia
- strabismus
- congenital glaucoma
- coloboma of the uvea
- systemically:
  - dysmorphic face

- growth abnormalities
- mental handicap

Congenital Anomalies of the Vitreous

Developmental Abnormalities of the Vitreous [8, 16]

- They are related to the presence of fetal vascular elements in the vitreous in the newborn, through incomplete regression of the hyaloid system, most cases being sporadic.
- Persistence of the pupillary membrane
  - it is common at birth, but may regress in the first weeks after birth.
- Persistence of the hyaloid artery
  - it can be isolated (rarely) or associated with persistence of hyperplastic primary vitreous
  - it presents as a cord from the papilla to the posterior lens capsule located in the Cloquet's canal
  - isolated forms are asymptomatic and do not require treatment.
- Persistence of hyperplastic primary vitreous (PHPV)
  - A very rare anomaly, it represents the persistence of the embryonic primary vitreous with the hyaloid arterial system and the posterior "tunica vasculosa lentis", unilaterally; it has two forms:
- anterior
  - more frequent
  - white pupil (leukocoria) and amaurosis at birth
  - ciliary processes drawn centrally and visible in the pupil
  - rarely membranous cataract; very rarely, cartilage development in the lens;
  - eye growth is delayed with microphthalmia and buphthalmia by blocking AH drainage
- posterior
  - retinal dysplasia, significant decrease in VA
  - "Morning glory" papilla
  - **Persistent *hyperplastic primary vitreous* (PHPV)—**clinically can have isolated or associated components.
- ***persistence of the hyaloid arterial system*** with variants:
  - isolated

- *Bergmeister's papilla*—is persistent, unresorbed glial fibrous tissue, located at the emergence of the fetal hyaloid artery on the optic disc located nasally; it can also take the appearance of a membrane on the surface of the optic disc—asymptomatic epipapillary membrane;
- posterior vitreous residues, which can lead to RD;
- prepapillary vascular loops (normal arteries)—can be complicated with retinal vascular obstructions, retinal hemorrhages.

- ***The persistence of the "vasculosa lentis tunic"*** with the persistence of the fetal vasculature is manifested by leukocoria; in severe forms it can be associated with microphthalmia, glaucoma, RD;
  - the transparent lens allows highlighting:

    white/yellow retinocrystalline tissue that may extend towards the papilla;
    Mittendorf points–remnants of the anterior part of the hyaloid artery, asymptomatic, which are opacities of the posterior capsule located 0.5 mm medially to the center;
    vitreous cysts—by abnormal resorption of the anterior or posterior hyaloid vascular system;
    the presence of the opaque lens requires ultrasound B to establish a positive diagnosis.

- Persistence of fetal vasculature may be associated with:
  - ocularly:

    microphthalmia
    posterior polar cataract
    chorioretinal colobomas
    Peters anomaly
    macular dysplasia

- systemically:

  trisomy 13 Patau
  trisomy 18 Edwards
  Walker—Warburg syndrome

Vascular Vitreoretinal Dystrophies [4]

- **Norrie disease**
  - it affects the eye, CNS, hearing;
  - ocularly:

    anterior pole abnormalities, iris hypoplasia, uveal ectropion
    retrolental fibroplastia
    peripheral vitreous and retinal abnormalities with RD

- **Incontinentia pigmenti**
  - ectomesodermal dysplasia, lethal in boys;
  - ocularly:

    persistence of pseudoglioma-like fetal vasculature with retinal dysplasia;
    nystagmus, strabismus, ptosis
    congenital cataract

  - systemically:

    affects the teeth, skin, NCS.

- **Familial exudative vitreoretinopathy**
  - bilateral, asymmetric, AD, with a wide clinical variety, similar to retinopathy of prematurity, but in the absence of prematurity;
  - abnormal development of the hyaloid vascular system with extensive portions of avascular retina in the temporal periphery, associated with arterio-vascular anastomoses and neovascular proliferations.

- **Isolated vitreoretinal dystrophies**
- ***Goldmann-Favre syndrome***
  - early onset (10 years old) with bilateral VA decrease, nyctalopia, peripheral narrowing of the visual field;
  - bilateral, symmetrical: pigment changes (RP), cystoid macular edema, posterior vitreous detachment, optic atrophy, cataracts.

- **Juvenile retinoschisis**
  - men, bilateral, AR with VA decrease in time;
  - ocularly:

- strabismus, nistagmus, hypermetropia;
- eye fundus:
  - inferotemporal peripheral retinoschisis, bilateral, asymmetric, which can extend with round or oval ruptures;
  - microcystic foveal changes

    complications: vitreous hemorrhages, retinal tears, rhegmatogenous retinal detachment;
    there is no treatment to stop progression, laser photocoagulation could reduce the risk of RD.

- **Wagner disease**
  - juvenile onset with progressive nyctalopia and narrowing of the peripheral VF
  - ocularly:

    high myopia
    early cataract;

degenerated vitreous with areas of fibrous, filamentous condensations and equatorial adhesions extending at retrocrystalline level;
areas of peripheral chorioretinal atrophy
complications—RD

– systemically

characteristic facies with epicanthus, nose with widened base, retrognathism.

Optic Disc Congenital Anomalies

- Congenital abnormalities of the papilla without neurological associations [3, 12]
  - ***Myelin fibers***—are given by the extension of the myelination process before the cribriform plate

    unilateral, rarely bilateral, asymptomatic
    white myelin arranged radially in the papilla
    may be associated with: polycoria, keratoconus, nystagmus, coloboma, congenital cataract, myopia, astigmatism
    systemic associations: neurofibromatosis, epilepsy, cranial dysostosis.

  - ***Papillary drusen—***is calcified hyaline material located in the papilla—nasal, bilateral, hereditary, familial;

    often asymptomatic, but there may be VF deficiencies with slow evolution (enlargement of the blind spot, VF constrictions);
    initially, the drusen is located deeply (slightly elevated optic disc, with erased outline, with pigmentary changes with the absence of physiological excavation), but in evolution, it can appear superficially with pearly irregularities at the edge of the papilla;
    possible eye associations: papillary vascular abnormalities;
    systemic associations: PR, *pseudoxanthoma* elasticum, angioid striae;
    superficial papillary, intravitreal, deep, hemorrhagic complications (rarely), choroidal neovascular membranes (CNVMs), anterior ischemic optic neuropathy (AAION) are possible.

  - Ttilted disc

    uni-, bilateral, asymmetric optic disc, small, oval, with oblique vertical axis oriented inferonasally (in the form of the letter D) with reduced papillary diameter with inferior depression and superior convexity;
    normal VA, VF with superotemporal defects (requires vertical meridian testing);
    ocular associations: myopic astigmatism;
    systemic associations: hypertelorism, Apert syndrome, Ehlers—Danlos.

– Optic pit

small excavation (often temporary);
asymptomatic or VA decrease with metamorphopsia.
Complications: serous RD

Congenital Anomalies of the Papilla Associated with Neurological Anomalies [3, 9, 12]

- ***Coloboma of the papilla*** (due to a defect in the closure of the embryonic fissure) includes three forms: tilted coloboma, isolated coloboma, retinochoroidal coloboma;

  – isolated coloboma

  asymptomatic or decreased VA
  upper VF changes with absolute scotoma
  color sense impairments
  eye fundus—enlarged inferonasal papilla, uni-, bilaterally, excavations in the form of a bright white bowl, with the visibility of the sclera;
  complications: serous RD, extension of excavation, rhegmatogenous retinal detachment (RRD)
  ocular associations: microphthalmia, other colobomas, refractive errors, strabismus, congenital cataract, hyaloid artery
  systemic associations: Patau syndrome (trisomy 13), Edwards syndrome (trisomy 18), trisomy 22.

- ***Syndromes associated with coloboma of the papilla*** [7]

  – ***Aicardi syndrome***

  ocularly:

  coloboma of the papilla ± iris
  cataract
  pupillary membrane
  microphthalmia

  systemically:

  malformations of the CNS, skeleton
  psychomotor retardation

  – ***Goldenhar syndrome***

  ocularly:

  conjunctival, corneal dermoid
  palpebral, iris, papillary coloboma
  microphthalmia

lacrimal-nasal canal obstructions

systemically

hypoplasia of facial bones
preauricular appendage
CNS, ear, vertebral anomalies

– ***Rubinstein—Taybi syndrome***

ocularly:

hypertelorism
congenital glaucoma
coloboma of the uvea
epicanthic fold
ptosis
strabismus

systemically

short stature
growth abnormalities without dysmorphism
mental retardation

– ***Walker—Warburg syndrome***

ocularly:

coloboma of the uvea
microphtalmia
cataract
Peters anomaly

systemically:

hydrocephalus
brain malformations
severe retardation
early death

- ***Hypoplasia, dysplasia, aplasia of the disc***
  - uni-, bilateral, non-progressive, with small optic disc (1/3–1/2)
  - asymptomatic or decreased AV
  - eye fundus– at the level of the "double ring" disc, depigmented halo surrounded by an externally pigmented border;
  - ocularly: afferent pupillary defect, aniridia, foveal hyperplasia, microphthalmia, strabismus, nystagmus, coloboma of the uvea
  - systemically: frontonasal dysplasia, cerebral and endocrine abnormalities.
- ***Morning glory***—it is a *funnel*-shaped *staphylomatous excavation* at the level of the optic disc

- ocularly:

  prominent or retracted enlarged optic disc within the staphyloma;
  the emergence of retinal vessels at the edge of the excavation (periphery of the disc) radially, like the spokes of a wheel, with numerous vessels;
  whitish glial tissue in the center of the papilla
  very low VA
  afferent pupillary defect
  VF changes (blind spot enlargement, central scotoma);
  ocular associations: amblyopia, anisometropia, strabismus, retinal detachment, megalopapilla, NO hypoplasia

  systemic associations: neurofibromatosis 2, craniofacial dysplasias;
  complications: serous RD.

- ***Other malformations of the papilla***

  - Megalopapilla

    increase in papillary diameter and excavation;
    normal VA, normal VF
    systemic associations: mandibulofacial dysostosis.

  - Double papilla

    mseparate papillae, or without separation (duplication, pseudopapilla) rarely.

  - Peripapillary staphyloma

    unilateral, rare, with normal papilla but lacking central glial tissue.

  - Pigmentation abnormalities of the papilla by accumulation with juxtapapillary pigment (in the crescent).

- ***Vascular anomalies of the papilla***

  - Vascular papillary loops (branches of CRA), can rarely be complicated with vitreous hemorrhages, hyphema, RVO
  - varicose veins - at vascular emergence - rarely
  - optociliary veins—shunt between CRV and choroidal circulation; they can be present in CRVO, chronic papillary edema, papillary drusen, ON glioma;
  - the cilioretinal artery irrigates the inter-papillo-macular area;
  - papilloretinal vascular abnormalities with changes in vascular pathway and caliber around the papilla.

Congenital Disorders of the Pupil

- Polycoria
  - multiple pupils that are actually holes in the iris sphincter;
  - essential iris atrophy—may be accompanied by glaucoma
  - Rieger's syndrome with iris hypoplasia
- Microcoria
  - rare, sporadic, unilateral
  - very small pupil; does not dilate
  - infectious antecedents in pregnancy should be sought;
  - it can be associated with glaucoma with angle dysgenesis, Axenfeld syndrome, Rieger syndrome, Recklinghausen disease.
- Persistence of the pupillary membrane
  - is a resorption anomaly of the anterior part of the vascular tunic of the lens;
  - normal VA
  - do not require treatment.

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Chapter 2
Ophthalmological Pathology of the Eye: Orbit

Marieta Dumitrache

Abstract Pathology of the orbit begins by presenting **changes in the position of the eyeball** in the orbit: proptosis and enophthalmia, with the presentation of their clinical characteristics. **Thyroid orbitopathy** (TO) associated in 90% with hyperthyroidism, is the most common cause of proptosis, which in TO is axial, nonpulsatile, reducible, permanent and exceeds 20 mm. Proptosis is accompanied by eyelid changes—exposure keratopathy, diplopia, restrictive myopathy, optic neuropathy. Treatment of TO requires interdisciplinary collaboration—endocrinologist/ophthalmologist. The most common **infectious inflammatory conditions of the orbit are preseptal and postseptal cellulitis** (orbital abscess), a condition that is an absolute ocular emergency, requiring immediate administration of injectable antibiotics, hospitalization and interdisciplinary control. **Primary orbital tumors, benign and malignant**, have multiple clinical forms, they can be cystic (dermoid cyst), vascular (capillary cavernous hemangioma), fibroma, fibrosarcoma, osteoma, osteoblastoma, Ewing sarcoma, optic nerve tumors and secondary and metastatic tumors.

Keywords Proptosis · Enophthalmia · Thyroid orbitopathy · Exposure keratitis · Diplopia · Restrictive myopathy · Preseptal and postseptal orbital cellulitis · Primary orbital tumors · Benign · Malignant · Secondary tumors · Metastatic tumors

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Position Changes of the Ocular Globe in the Orbit

Proptosis

Proptosis (exophthalmos) is the anterior displacement of the eyeball, in front of the bony frame of the orbital rim, by increasing the volume of the retroocular structures (the orbit is a cavity with inextensible walls) or, more rarely, due to a shallow orbit [1].

The normal position of the eye within the orbit is related to the position of the tip of the cornea in relation to the plane of the lateral canthus and is below 18 mm.

Exophthalmos is measured with a Hertel exophthalmometer—it is read on a scale, the tip of the cornea is visualized in a mirror, **values above 20 mm indicate the existence of an exophthalmos:**

- mild exophthalmos 21–23 mm;
- moderate exophthalmos 24–27 mm;
- severe exophthalmos over 28 mm, when it can be associated with exposure keratopathy.

Exophthalmos is [2]:

- axial—lesions in the muscle cone, optic nerve tumors;
- lateral—extraconical lesions: maxillary sinus tumors, dermoid cyst, lacrimal gland tumors, mucocele, fronto-ethmoidal carcinoma;
- pulsatile—carotid-cavernous fistula—CCF;
- reductible—Basedow disease or irreducible—large tumors; symmetrical or asymmetrical; frequently permanent, intermittent
- pseudoexophthalmos due to facial and orbital asymmetry, enlargement of the eyeball in high myopia, buphthalmia, palpebral retraction.

Unilateral proptosis is [3] (Table 2.1):

- congenital: dermoid cyst
- inflammatory
  - acute inflammatory infectious: orbital cellulitis, abscess, thrombophlebitis, cavernous sinus thrombosis—CST
  - chronic: pseudotumors, myositis, lymphoma, sarcoidosis, Crohn's disease, Wegener's disease, Churg Strauss angiitis
  - Tolosa-Hunt painful ophthalmoplegia with: inflammatory exophthalmos, recurrent painful ophthalmoplegia, alternating with inflammatory infiltration of the cavernous sinus (retrobulbar pain) upon awakening, very intense with brutal onset.
  - circulatory disorders and vascular lesions in: angioneurotic edema, orbital varices, aneurysm.
  - traumas—orbital hemorrhage, intraorbital foreign body, orbital emphysema
  - primary, secondary orbital tumors

Table 2.1 Unilateral and bilateral proptosis

	Infections	Inflammations	Tumors	Other
Unilateral proptosis				
Child	Orbital cellulitis	–	• Benign; dermoid hemangioma • Malignant: retinoblastoma, optic nerve glioma rhabdomyosarcoma	• Encephalocele • Orbital venous anomalies
Adult	Orbital cellulitis	• Dysthyroid orbitopathy • Orbital pseudotumor	• Optic nerve glioma • Optic nerve meningioma • Metastases	–
Bilateral proptosis				
	Infections	Inflammations	Tumors	Other
Child	–	• Pseudotumors	• Acute myeloid leukemia • Metastases from neuroblastoma • Histiocytosis	• Small orbits
Adult	• Cavernous sinus thrombophlebitis	• Dysthyroid orbitopathy • Orbital pseudotumor • Wegener's granulomatosis	• Iymphomas • Orbital lymphoid tumors	–

– frontal paranasal sinus mucocele (more commonly ethmoidal, maxillary mucocele).

Bilateral proptosis

- congenital: craniofacial dysostosis, oxycephaly
- osteopathies: osteitis deformans, acromegaly
- inflammatory: thyroid ophthalmopathy, Mikulicz syndrome, late stage, cavernous sinus thrombosis, carotid-cavernous fistula, orbital pseudotumor
- symmetrical tumors: lymphoma, lymphosarcoma, secondary tumors, neuroblastoma, Ewing sarcoma, leukemic infiltration, multiple myeloma
- systemic diseases: amyloidosis, xanthomatosis, Wegener's granulomatosis

Acute proptosis—rapid onset and is produced by: orbital emphysema, medial orbital wall fracture, orbital hematoma.

Intermittent proptosis is present in: orbital varices, orbital edema, vascular tumors.

Pulsatile proptosis can be present in carotid-cavernous fistula, saccular aneurysm of the ophthalmic artery, meningocele, meningoencephalocele, neurofibromatosis.

Severe proptosis can cause exposure keratopathy.

False proptosis:

- dysthyroid eyelid retraction, sequelae of facial paralysis
- large eyeball in strong myopia, buphthalmia
- contralateral enophthalmos

Proptosis with orbital signs:

- inflammations—orbital cellulitis
- dysthyroid orbitopathy

Proptosis due to tumor:

- optic nerve tumors: glioma, meningioma
- vascular lesions—cavernous hemangioma, capillary hemangioma, orbital varices, arterio-venous malformations
- damage to the oculo-motor muscles—lymphoma, metastases
- damage to the lacrimal gland, lymphoma
- damage to the bone wall—spheno-orbital meningioma
- tumors with orbital location—metastases, lymphoma, rhabdomyosarcoma, dermoid cyst, schwannoma, neurofibroma
- mucocele

Proptosis in young children

- capillary hemangioma (most frequently)—histiocytosis
- orbital cellulitis—leukemia
- dermoid cyst—retinoblastoma
- encephalocele—craniofacial dysgenesis

Proptosis in children

- orbital cellulitis (most frequently)—granulocytic sarcoma
- capillary hemangioma—retinoblastoma with orbital extension
- chist dermoid—optic nerve glioma
- orbital pseudotumor—lymphoma/leukemia
- lymphangioma—meningioma
- metastatic neuroblastoma

Proptosis in adults

- thyroid ophthalmopathy 50%
- hemangioma
- orbital pseudotumor

Enlargement of oculomotor muscles on CT scanner

- thyroid ophthalmopathy acromegaly
- orbital pseudotumor amyloid
- neoplastic metastases histiocytoma
- lymfoma Tenon's cyst
- infections Wegener's
- CCF granulomatosis

Unilateral periorbital swelling

- dermoid cyst rupture leukemia
- rhabdomyosarcoma eosinophilic granuloma
- orbital pseudotumor

Enophtalmia

- orbital wall fracture
- sclerosing metastatic tumors (carcinoma, sarcoma)

Painless proptosis

- cavernous hemangioma rhabdomyosarcoma
- optic nerve tumor histiocytoma
- neurofibroma lymphoma
- neurolemmoma osteoma

Painful proptosis

- orbital pseudotumor nasopharyngeal
- posterior scleritis carcinoma
- dacryoadenitis lymphangioma
- orbital hemorrhage orbital abscess
- lacrimal gland malignant tumor Wegener's
- orbital, lacrimal tumors granulomatosis
- meningioma, optic nerve glioma
- rhabdomyosarcoma

- Imaging investigations
  - X-ray radiography
  - ultrasound:

    mode A for measuring the optic nerve, muscles in Graves' disease
    mode B for orbital structures
    computed tomography (CT) to determine the location and size of the orbital mass

  - MRI

Enophthalmos

Enophthalmos is the displacement of the posterior part of the eye, pushing the eyeball into the orbit, and reducing the content of the orbit or increasing the cavity space.

Unilateral enophthalmos

- post-traumatic, in severe fractures, with clogging of the orbital walls cicatrizing orbital lesions
- cervical sympathetic palsy (Claude Bernard-Horner)
- atrophy of orbital contents secondary to radiotherapy, scleroderma**Bilateral enophthalmos**
- cachestic diseases: diabetes, cancer
- serious general infections: typhoid fever
- dehydrating conditions: cholera, dysentery

Thyroid Associated Orbitopathy

It is the most common cause of uni- or bilateral exophthalmos in adults with progressive evolution, more frequently encountered in women (*F*/*M* = 4/1), rare in men, with severe and very serious evolution in the elderly [4].

It is produced by a specific autoimmune reaction (through IgG antibodies) that causes an increase in intraorbital fat and hypertrophy of the extraocular muscles.

The onset of orbitopathy is congestive, inflammatory, generally with a regressive evolution in 3–4 years and is followed by the fibrotic stage, which can sometimes be associated with ocular motility disorders.

Classification of changes in thyroid orbitopathy NOSPECS.

Grade 0. NO—no sign.
Grade 1. ONLY—only palpebral retraction sign.
Grade 2. SOFT TISUE—periorbital edema.
Grade 3. PROPTOSIS.
Grade 4. EXTRAOCULAR MUSCLE with diplopia.
Grade 5. CORNEA—damaged due to exposure.
Grade 6. SIGHT LOSS—due to optic nerve compression.

Clinical forms:

- **Thyrotoxic proptosis–Graves' disease presents** [5]:
  - Signs of systemic hyperthyroidism: tremors, nervousness, irritability, weight loss, sweating, fatigue, tachycardia, heat intolerance, increased MB
  - goiter
  - pretibial myxedema
  - present in women 20–40 years of age.
- **Thyrotropic proptosis**

Thyrotropic proptosis affects middle age, tends to be self-limiting, with remissions and exacerbations.

- Stages of the evolution of thyroid orbitopathy:

  - congestive (inflammatory with regressive evolution in about 3 years)
  - fibrotic, possibly associated with ocular motility disorders

- Symptoms:
  - retrobulbar discomfort
  - photophobia
  - lacrimation
- Ocular signs: conjunctival hyperemia, chemosis, palpebral edema, periorbital edema, superior limbic keratoconjunctivitis
- Systemic signs:
  - hyper-, hypothyroid function
  - goiter in Graves' disease
  - pretibial myxedema, tachycardia in Graves' disease
  - other autoimmune conditions present: diabetes, Addison's disease

Symptoms of an overactive thyroid gland: fast pulse, warm, dry skin, enlargement of the thyroid gland (goiter), weight loss, hand tremors.

Symptoms of thyroid ophthalmopathy [6, 7]:

- decreased tear production associated with: dry eye, tearing, foreign body sensation, sensitivity to light, blurred vision
- eyelid retraction with exophthalmos, staring eyes, blinking difficulty, corneal dryness
- retroocular edematous imbibition of orbital muscles and fat with proptosis
- inflammation of the orbital tissue with edema and redness
- exposure keratopathy
- decreased vision through optic nerve compression, + visual field changes

Clinical Signs [8–10]

Proptosis is the most frequent sign present in: 63% of cases, unilateral or bilateral, symmetrical or asymmetrical, of variable severity.

Proptosis is axial, nonpulsatile, reducible, permanent, and exceeds 20 mm.

Palpebral changes include [11]:

Upper eyelid retraction with:

- ***Dalrymple's sign***—retraction of the upper eyelid with widening of the palpebral fissure
- ***von Graefe's sign***—oculopalpebral asynergy
- ***Stellwag's sign***—decrease in the frequency of palpebral blinking
- ***Enroth's sign***—edematous infiltration of the eyelid
- ***Gifford's sign***—the difficulty of eversion of the upper eyelid secondary lagophthalmos.

Soft tissue involvement related to edematous infiltration with hyperaemic conjunctiva with inferior conjunctival chemosis and superior limbic keratoconjunctivitis.

Exposure keratopathy by upper lid retraction, proptosis, lagophthalmos, decreased blinking rate

- corneal dryness, superficial punctate keratitis up to perforated corneal ulcer is present.

Optic neuropathy—rare but very serious, uni-, bilateral, by optic nerve compression with papillary edema and finally, optic atrophy with decrease/loss of vision.

Restrictive myopathy

Möbius sign with weakening of convergence, with more frequent involvement of the inferior rectus muscle.

Diplopia due to myositis inflammatory process.

TO treatment requires interdisciplinary collaboration between endocrinologist and ophthalmologist [10, 12, 13].

- **in the congestive stage:** artificial tears, lubricating ointments, blepharorrhaphy (if necessary), Fresnel prisms in diplopia
- in the advanced stage, **orbital radiotherapy 15–30Cgy surgery for orbital decompensation** may be necessary
- **treatment of hyperthyroidism**
- **surgery of the extraocular muscles** for the correction of strabismus and diplopia: tarsorrhaphy, rectus inferior recession, Mülerectomy
- **eyelid surgery**
  - treatment of proptosis
  - corticoid treatment:
  - oral prednisolone 60–80 mg/day 1 week, progressively decreasing to 3 months

    methylprednisolone 500 mg/day i.v. in 200 ml isotonic solution—3 consecutive days 4 cycles in 4 weeks—cumulative dose—6 g
    methylprednisolone 1 g/day i.v.—3 days, followed by oral corticosteroids 1 mg/kg/day with progressive decrease for 2 months

  - immunosuppressive treatment

    cyclosporine in unresponsive TO or optic neuropathy azathioprine, methotrexate, rituximab.

TO in the non-inflammatory (dysthyroid) phase [14]

- Clinically
  - axial exophthalmos, reducible, initially unilateral, which quickly becomes bilateral
  - oculomotor disorders with decreased abduction and elevation by preferentially affecting the medial and inferior rectus muscles
  - palpebral retraction with oculopalpebral asynergy
- Signs of gravity
  - optic neuropathy

  - corneal exposure
  - ocular hypertension

- CT diagnosis

  - muscular form—with thickening of the oculomotor muscles: rectus inferior, rectus medial, rectus superior, rectus lateralus with enlargement of the tendons at insertion
  - the fatty form with retroorbital fat hypertrophy without affecting muscle mass
  - mixed forms

TO in inflammatory stage [9, 14]

It is more common in the first 2 years, when orbitopathy also occurs.

Clinically—eye pain, conjunctival hyperemia, chemosis, aggravation of exophthalmos, diplopia, decreased VA

- artificial tears, sunglasses
- in severe forms—hospitalization
- solumedrol bolus then cortancyl + orbital radiotherapy
- Treatment in TO (Table 2.2)

Malignant edematous exophthalmos

It can occur after thyroidectomy or radioactive iodine treatment and is a rare but serious complication.

Clinically—rapid major, painful, irreducible exophthalmos, accompanied by oculopalpebral signs with chemosis and oculomotor deficit.

It can be complicated by corneal hypoesthesia, corneal ulcer and abscess, and edematous optic neuropathy.

Emergency corticotherapy + orbital radiotherapy + tarsorrhaphy + orbital decompression required.

The use of Neosynephrine is contraindicated, risk of anterior dislocation of the globe.

Infectious Inflammatory Diseases of the Orbit

Classification [16].

- Acute

  - preseptal cellulitis
  - postseptal and orbital cellulitis—intraorbital abscess
  - orbital osteoperiostitis
  - orbital thrombophlebitis
  - tenonitis
  - cavernous sinus thrombosis

- Chronic

Table 2.2 Treatment in TO [12, 15]

Orbital tissue involvement	Palpebral retraction	Exophthalmos	Optic neuropathy	Myopathy	Diplopia	Exposure keratitis
• Artificial tears • Contact lenses • Moisture chamber	• Muscle surgical treatment • Orbital decompression • Blepharoplasty	• Systemic corticosteroids • Immunosuppressants • Radiotherapy • Orbital decompression	• i.v. corticosteroids • Immunosuppressants • Radiotherapy • Orbital decompression	• Corticosteroids • Irradiation • Oculomotor muscle surgery • Botulinum toxin	• Steroids • Prisms • Strabismus surgery	• Lubricants • Artificial tears • Occlusion of the lacrimal puncta • Tarsoraphia

- specific: tuberculosis, syphilis, actinomyces, mycotic infections/mucormycosis, parasitic infections
- nonspecific: orbital pseudotumor

Preseptal Cellulitis

Preseptal cellulitis is the inflammatory edema of the subcutaneous cellular tissue located in front of the orbital septum.

It does not affect the content of the orbit, being a previous inflammation and **evolves without altering the visual function.**

Preseptal cellulitis and orbital cellulitis are clinically distinct diseases, but they are causally produced by approximately identical factors [17, 18].

The usual causative organisms are: Staphylococcus aureus and pyogenic streptococcus by exogenous infection in a skin wound, insect bite, extension from a local infection (organitis, dacryocystitis) or endogenously, by septic metastasis from an ear infection or respiratory infection (infection with hemophilus—purple eyelid in a child).

- Clinically:
  - Subacute onset with periocular discomfort and edema, palpebral redness, malaise, fever in child
  - edematous eyelid (redness, warmth, pain), palpebral fissure opens with difficulty
  - **exophthalmos, diplopia, painful ophthalmoplegia are absent.**
- Treatment
  - Antibiotic—augmentin in children 30 mg/kg/day × 3/day; in adults 875 mg × 2/day
  - Treatment of sinusitis, respiratory infection.

Postseptal Orbital Cellulitis (Intraorbital Abscess)

Orbital cellulitis is the infection of the orbital contents behind the orbital septum that may progress to a subperiosteal abscess or orbital abscess [19, 20].

Etiologically, orbital cellulitis is produced by:

- extension of a preseptal cellulitis
- exogenous infection from the perforating wound, intraorbital foreign body retention, postoperatively
- extension of an infection from teeth, face, paranasal sinuses, orbital cavity, intracranial

- metastatic endogenous infection from breast abscess, puerperal sepsis, leg thrombophlebitis, septicemia; causative agents are: streptococcus pneumonia, staphylococcus aureus, pyogenic staphylococcus, hemophilus influenza

Acute onset with fever, eye pain, rapid loss of vision, diplopia, malaise.

Laboratory examination: culture (in febrile states) with antibiogram, nasal exudate.

Imaging examination in the presence of ocular signs: chemosis, proptosis, restricted eye movements, relative afferent pupillary defect (RAPD), optic nerve edema, repeated at 36–48 hours (under i.v. antibiotic).

Sinuses X-ray.

- Clinically
  - the signs of preseptal cellulitis much more intense with: inflammatory palpebral, periorbital edema, red, warmth, in tension, intense conjunctival chemosis, closed palpebral fissure to which the following are added:
  - proptosis masked by palpebral edema more commonly lateral and downward
  - painful ophthalmoplegia
  - signs of compression optic neuropathy with RAPD, papilledema, optic atrophy
  - general signs—fever, headache, lethargy, suspected meningitis
- Complications
  - ocular: ocular hypertonia, endophthalmitis, exposure keratopathy, occlusion of central retinal artery (ram), optic neuropathy
  - spread of infection: meningitis, brain abscess, TSC, orbital and subperiosteal abscess
- Suspicion of evolution of preseptal cellulitis into posterior cellulitis:
  - fever
  - immunocompromised patient
  - child <12 months
  - patient under oral antibiotic treatment for 36–48 h with worsening symptoms and signs

Emergency elements in orbital cellulitis are related to the accentuation of diagnostic clinical signs: orbital pain, proptosis, sharp decrease in vision.

Permanent clinical evaluation of the evolution of orbital cellulitis, MRI, CT, blood culture.

Hospitalization with ophthalmological, ENT, neurological supervision.

Diagnosis differentials—preseptal cellutis, orbital cellulitis (Table 2.3)

The treatment of orbital cellulitis is an absolute emergency, with hospitalization under injectable antibiotics and interdisciplinary check-up.

- Treatment
  - Analgesic, anti-inflammatory, antibiotic treatment (Table 2.4)

Table 2.3 differential diagnosis–preseptal/orbital cellulitis

Clinical signs	Preseptal cellulitis	Orbital cellulitis
Fever	No	Yes
Eyelid edema	+	+++
Chemosis	±	+++
Limited, painful eye motility	Normal	Da
VA	Normal	Decreased
Proptosis	−	+
Optic nerve edema	No	Yes
DPAR	Normal	Present

Table 2.4 Current antibiotic treatment recommendations in orbital cellulitis

	I.V. intravenously	Orally	Duration
Orbital cellulitis Severe cellulitis	• Cephalosporin – Cefotaxime – Ceftriaxone + • Flucloxacil 50/kg i.v. at 6 hours or • Vancomycin in case of MRSA – Duration depending on the clinical aspect	• Amoxicillin with • Clavulanic acid	10–14 days
Moderate periorbital cellulitis	• Ceftriaxone • Clindamycin Or • Trimethropin with sulfamethoxazole	• Amoxicillin with • Clavulanic acid	8–10 days
Mild periorbital cellulitis	–	• Cephalexin Or • Cefuroxime	7–10 days

i.v.

Vancomycin 500 mg i.v. at 6 hours
Cephalosporins generation 3 i.v. = 10–14 days
Clindamycin i.v.

Orally

Ceftazidime i.m. and oral Metronidazole

– Interdisciplinary clinical monitoring: ophthalmologist, ENT physician, neurologist.
– Surgical treatment in case of antibiotic treatment failure, vision loss, orbital or subperiosteal abscess with evacuation of pus from the orbit and drainage of the paranasal sinuses

Tenonitis

It is inflammation of Tenon's capsule and has two clinical forms [16]:

Serous form is the local manifestation of a general infection: acute articular rheumatism, scarlet fever or in the presence of foci of infection in the body

- Clinically—eye and periocular pain accentuated by eye movements, conjunctival chemosis
- Benign evolution with possible recurrence and bilateralization
- Treatment—corticosteroid therapy

The suppurating form from infected wounds, orbital infections

- Clinically—chemosis, accentuated exophthalmos, immobile eye, painful at eye movements, decreased vision.
- Complications—uveitis, papilledema.
- Treatment—antibiotics

Orbital Mucormycosis

It is a very rare opportunistic infection produced by a fungus from the rhizopus species of the Mucoracee family (present in decomposition) that affects immunocompromised patients (transplantation, malignant tumors, immunosuppressed patients under prolonged cortisone treatment, diabetics).

Clinically, onset with progressive facial and periorbital edema—conjunctival chemosis, blurring, decrease of vision, diplopia, ophthalmoplegia, black ulcers and suppurations of the eyelids, palatal mucosa, nasal septum.

Complications: cranial nerves paralysis, cerebrovascular occlusions.

Difficult treatment, often ineffective requiring rapid correction of metabolic imbalances.

- antifungal treatment—Amphotericin B i.v., Posaconazole
- early, aggressive surgical treatment with debridement, amphotericin dressing, excision in healthy tissue with removal of necrotic tissue
- exenteration as needed

Cavernous Sinus Thrombosis: CST

Each cavernous sinus contains—the cranial nerves—III, IV, VI, V_1, V_2, carotid sympathetic plexus, intracavernous carotid artery.

CST is aseptic and septic which is a serious, potentially fatal complication starting in the paranasal sinuses, ear, teeth, through retrograde infection through the avalvular veins.

- anterior—the infection is transmitted from the paranasal sinuses, face, orbit through the ophthalmic vein
- posterior—the infection from the mastoid is transmitted through the labyrinthine mastoid emissary veins
- upper—infection from meningitis, brain abscess
- medial—communication between the two sinuses [21, 22]

CST has a unilateral onset, in 50% of cases, it becomes bilateral with severe eye pain, photophobia, chemosis, decreased vision, RAPD, semi-mydriasis with slow RFM with eye fundus changes: papillary edema, retinal hemorrhages.

- General signs—**edema in the mastoid region**, pathognomonic, tachycardia, high fever, intense headache, neck stiffness, seizures, coma.

Aseptic TSC is associated with: trauma, nasopharyngeal cancer, skull base tumors.

- Immediate treatment—prolonged monitoring
  - broad-spectrum i.v. antibiotic 3–4 weeks
  - anticoagulant—heparin (controversial)
  - steroids (controversial)
  - surgical treatment if needed.

Non-infectious Inflammatory Diseases of the Orbit

Orbital Pseudotumor

It is a chronic idiopathic inflammation of the orbit more often in obese women 40–50 years old, with poor socioeconomic status, with spontaneous remission, intermittent episodes, with possible recurrences, progressive fibrosis and ophthalmoplegia [23].

- Clinical manifestations are variable depending on the location and evolution of the inflammatory process with congestive exophthalmos and ophthalmoplegia.
- It requires differential diagnosis with: orbital cellulitis, Wegener's granulomatosis, orbital tumor.
- Treatment
  - systemic corticosteroid therapy, effective in 50–75% of cases,1 mg/kg/day
- Radiotherapy in the patients who are unresponsive to drug therapy.
- in corticosteroid-resistant forms—methotrexate, cyclophosphamide, infliximab.

Acute Dacryoadenitis.

It is the acute idiopathic inflammation of the lacrimal gland through localized inflammation or occurring in systemic determinations: sarcoidosis, Mikulicz syndrome, syphilis, lymphoma [24].

- Clinically:
  - edema, redness, in the region of the lacrimal gland
  - S-shaped lid
  - downwards eyeball dystopia
  - lacrimal gland hypertrophy

  - limited eye motility
  - fever
- Treatment—corticotherapy; cytostatics if needed

Orbital Myositis

It is the isolated non-specific idiopathic inflammation of one or more extraocular muscles, often bilateral, with onset at the age of 30, with ocular pain exacerbated by eye movements and diplopia.

Clinically—moderate congestive exophthalmos, increased pain on movement in the direction of the affected muscle, chemosis, diplopia, ptosis with **spindle-shaped thickening of the affected muscle.**

Variable evolution with: spontaneous resolution, chronic evolution, relapse, restrictive myopathies.

Treatment—NSAIDs, corticotherapy (does NOT prevent relapses), radiotherapy.

Tolosa Hunt Syndrome

It is the non-specific granulomatous inflammation located in the cavernous sinus, superior orbital fissure and/or apex of the orbit.

Onset with diplopia and painful hemicrania.

Clinically—moderate exophthalmia, painful ophthalmoplegia, loss of sensitivity in V_1, V_2 cranial nerves.

Treatment—systemic corticosteroid therapy.

Wegener's Granulomatosis

It is a systemic necrotizing vasculitis associated with inflammatory granulomatosis at the level of the orbit extending from the paranasal sinuses, nasopharynx.

Clinically—congestive exophthalmos and ophthalmoplegia, often bilateral associated with dacryoadenitis and lacrimal-nasal obstruction.

Treatment—cyclophosphamide and systemic corticosteroids may be effective.

Vascular Lesions

Orbital Varices

They are segmental dilations of the orbital veins of variable length and complexity, located more frequently superonasally.

- Clinical signs
  - intermittent, nonpulsatile exophthalmia, without bruits, accentuated during the Valsalva test
  - eyelid and subconjunctival lesions
  - eye motility disorders (possibly diplopia)
- Complications
  - bleeding
  - thrombosis
- Treatment—surgical excision (rarely) in recurrent thrombosis, painful varices, large exophthalmos, optic nerve compression.

Carotid-Cavernous Fistula

- It is an abnormal communication between artery and vein through two mechanisms:
  - post-traumatic
  - spontaneously in elderly women

Direct Carotid-Cavernous Fistula

It is a high blood flow shunt, blood that passes directly from the carotid artery into the cavernous sinus through an opening in the wall of the intracavernous portion of the internal carotid artery (ICA).

- Causes:
  - skull base fracture with intracavernous ICA rupture
  - spontaneous rupture of an intracavernous carotid aneurysm or an atherosclerotic artery.
- Clinical signs
  - sudden onset by trills given by intracranial fluid flow
  - pulsatile exophthalmos associated with a temporal murmur and synchronous trill that may disappear upon compression on the ipsilateral carotid at the level of the neck
  - dilatation of conjunctival vessels
  - chemosis with a “jellyfish head” appearance
  - increase in intraocular pressure
  - anterior segment ischemia
  - frequent oculomotor paralysis in the VIth cranial nerve

  - eye fundus: papillary edema, venous dilatations, retinal hemorrhages.

FAG is required to confirm the diagnosis.

- Treatment—interventional radiology with balloon occlusion of the fistula.

Indirect Carotid-Cavernous Fistula: Dural Shunt

It is a low-flow shunt in which arterial blood passes through the meningeal branches of the ECA or ICA indirectly into the cavernous sinus.

- Causes
  - congenital malformations complicated with vascular thrombosis
  - spontaneous rupture or favored by minor trauma or exertion
- Clinical signs
  - progressive onset with redness in both eyes with dilated episcleral and conjunctival vessels
  - ocular pulsations
  - ocular hypertension
  - moderate exophthalmos, sometimes the presence of bruits
  - oculomotor paralysis, more frequently in the VIth nerve
  - eye fundus can be normal or with moderate venous dilatations.
- Treatment
  - Many fistulas can close spontaneously
  - Surgical treatment in: diplopia, rebellious headache, large exophthalmos, exogenous glaucoma

Orbital Tumors [25]

Primary Tumors

Cystic tumors—dermoid cyst, epidermoid cyst, mucocele, encephalocele.
Vascular tumors—capillary cavernous hemangioma, lymphangioma.
Adipose tumors—liposarcoma.
Fibrous tumors—fibroma, fibrosarcoma.
Bone tumors—osteoma, chondroma, osteoblastoma, osteogenic sarcoma after irradiation, fibrous dysplasia, Ewing sarcoma.
Myomatous tumors—rhabdomyoma, rhabdomyosarcoma.
Optic nerve and sheath tumors—glioma, meningioma.
Lacrimal gland tumors—benign, mixed malignant, lymphoid tumors.

Benign, malignant lymphocytic tumors.
Secondary tumors.
Metastatic tumors.

Primary Tumors

Dermoid cyst—benign cystic teratoma, with abnormal ectodermal presence at the embryonic suture lines (contain hair follicles and sebaceous gland)—there are two forms:

- simple—superficial in a child, with a subcutaneous, mobile nodule, located supero-temporallytreatment: excision
- deep—onset in adolescent, adult with exophthalmos, dystopiatreatment—excision.

Mucocele

It is a slow-growing cystic accumulation with mucoid secretions and epithelial debris generated by an obstruction in the drainage of the paranasal sinuses.

- Clinically—exophthalmos with dystopia, upper palpebral and periorbital edema.
- Surgical treatment with the restoration of normal drainage of the sinuses

Encephalocele

It represents the herniation of the intracranial content crossing a congenital fissure at the base of the skull with onset in childhood, with the displacement of the eyeball anterolaterally or downwards, with pulsating exophthalmia without bruits, possibly associated with bone anomalies (hypertelorism, cleft palate), ocular (microphthalmia, coloboma), neurofibromatosis type 1 (associated with posterior encephalocele).

Capillary hemangioma—present at birth with lesions in the upper anterior portion, ptosis, diplopia. Initially, the tumor can grow up to 1 year followed by stabilization, regression, disappearance.

Treatment according to evolution, location: intralesional corticosteroids, resections, radiotherapy.

Cavernous hemangioma—orbital tumor located in the retrobulbar space in the muscular cone, benign in adults, 70% of cases occurring in women, with onset at age of 40–50, with slowly progressive axial non-congestive unilateral

exophthalmos, complicated with papillary edema, choroidal folds, by compression on the apex of the orbit.

Treatment—surgical excision.

Pleomorphic adenoma of the lacrimal gland is the benign mixed tumor, the most common epithelial tumor of the lacrimal gland.

Onset around the age of 50 with painless superotemporal palpebral edema, with hypertrophy of the lacrimal gland, inferonasal dystopia—surgical treatment with excision of the tumor.

Lacrimal Gland Carcinoma

Onset at 40–60 years old, rapid evolution with inferonasal dystopia, hypoesthesia, periorbital edema, requiring radical surgery with associated radiotherapy. Poor prognosis.

Optic nerve glioma is a benign tumor with onset around the age of 10 with progressive unilateral loss of visual acuity, exophthalmos, optic nerve dysfunction with papillary edema and fusiform enlargement of the optic nerve.

MRI may show intracranial extension.

It may be associated with neurofibromatosis type 1.

Treatment requires excision of the tumor with preservation of the eyeball.

the tumor with intracranial extension requires neurosurgical treatment.

inoperable cases could benefit from radiotherapy.

Meningioma—is an invasive tumor with two types:

Primary intraorbital meningioma—or **optic nerve (ON) sheath meningioma** producing early visual loss associated with limitation of eye movements, papill-edema or optic atrophy and slowly progressive unilateral proptosis; tubular thickening and optic nerve calcification is present.

treatment—tumor surveillance, surgical excision.

Secondary orbital meningioma—is an intracranial meningioma with secondary orbital invasion, starting from the sphenoid bone.

proptosis and significant decrease in vision are present.

neurosurgical treatment.

Plexiform neurofibroma—with onset in the first decade with periorbital edema with S-shaped upper eyelid deformation.

Association with neurofibromatosis type 1 may be present.

Surgical treatment should be well quantified if performed.

Lymphoma—is a malignant tumor of lymphoreticular origin subdivided into two types with progressive growth and risk of dissemination: Hodgkin's and non-Hodgkin's lymphoma (more commonly orbital tumor), with onset in young people.

Treatment—radiotherapy for localized tumors and chemotherapy for disseminated forms.

Rhabdomyosarcoma is a primitive malignant orbital tumor with rapidly progressive exophthalmos, which may mimic an inflammatory process.

The tumor is most frequently located in the retrobulbar space; it is rapidly progressive with evolution in the superonasal quadrant in children of 7–8 years old.

Clinically:

- Proptosis.
- Tumor + inflammation.

Alteration of general condition.

Emergency orbital scanner.

Emergency orbital biopsy under general anesthesia.

Treatment.

Radiotherapy combined with systemic chemotherapy with vincristine 2 mg/m^2, actinomycin D, cyclophosphamide.

Exenteration as needed.

Secondary Tumors

Tumors of the eyeball—retinoblastoma, malignant melanoma.

Tumors of the eyelids—squamous and basal cell carcinoma.

Paranasal sinus tumors—with orbital invasion: carcinoma, sarcoma, osteoma.

Nasopharyngeal tumors—carcinoma.

Tumors of the cranial cavity or invading the orbit—glioma, meningioma.

Metastatic Tumors

Neuroblastoma—from the sympathetic chain.

Nephroblastoma—from the kidney.

Carcinoma—from lungs, breasts, prostate, thyroid, rectum.

Malignant melanoma—from the skin.

Metastatic Tumors in Children

Neuroblastoma—is the most common tumor in children developed from primitive neuroblasts of the sympathetic chain, abdomen, thorax, pelvis, with onset in young children, manifested by fast-growing superior orbital tumor and palpebral ecchymosis (sometimes bilateral).

Granulocytic sarcoma (chloroma)—is a localized tumor, with onset in the first 10 years of life, with rapidly progressive exophthalmos, sometimes bilateral.

Langenhans cell histiocytosis—characterized by destructive inflammatory lesions in bone, soft tissue, in a child with typical superotemporal osteolytic lesions.

Metastatic tumors in adults.

Metastases from the bronchi, breasts, prostate, skin, digestive tract, kidneys.

Treatment—radiotherapy.

Orbital invasion from maxillary, ethnoid, nasopharyngeal carcinoma.

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Chapter 3
Ophthalmological Pathology of the Eye: Lacrimal System

Marieta Dumitrache and Miruna Cioboata

Abstract Infectious-inflammatory diseases of the lacrimal gland are **acute and chronic dacryoadenitis**, primary or secondary, of local or systemic cause**. Dacryocystitis is the acute or chronic** inflammation of the lacrimal sac, associated with obstruction of the nasolacrimal canal. Congenital dacryocystitis occurs in the new-born due to incomplete perforation/imperforation of Hassner's membrane at birth and nasolacrimal obstruction. **Congenital dacryocystitis** often has a **chronic** course that can become **acute** with inflammatory phenomena, located at the level of the lacrimal sac. The treatment of the chronic form of congenital dacryocystitis is tear ducts probing with nasolacrimal desobstruction, the acute dacryocystitis requiring antibiotic treatment and the incision of the lacrimal sac. **Adult dacryocystitis is chronic** and requires surgical treatment by dacryocystorhinostomy. **Dry eye syndrome** with Sikka keratoconjunctivitis is produced by insufficient tear secretion (Sjogreen syndrome) or secondary, in autoimmune diseases (juvenile arthritis, multiple sclerosis, dermatomyositis LES), evaporative dry eye in posterior blepharitis, proptosis or preserved tear secretion but excessive evaporation of tears, tumors, scars, NC VII paralysis. **Hyperlacrimation** is primary (rare), in tumors, reflex in inflammatory pathology of the anterior pole (blepharitis, conjunctivitis, iridocyclitis, acute glaucoma) or central (emotional). The clinical evaluation of lacrimation is done by the Jones I–II test.

Keywords Chronic acute dacryoadenitis · Chronic congenital dacryocystitis · Nasolacrimal imperforation · Lacrimal duct adult dacryocystitis · Acute

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dacryocystitis with peridacryocystitis · Adult dacryocystitis · Dacryocystorhinostomy · Lacrimal probing · Sika keratoconjunctivitis · Evaporative dry eye · Hyperlacrimation · Johns I and II test

Dacryoadenitis

- It is the inflammation of the lacrimal gland isolated or within the framework of systemic diseases because of…
  - infectious through bacterial infections (Staphylococcus Aureus, Streptococcus, Hemophilus, Pseudomonas, Chlamydia Trachomatis), viral infections (Epstein Barr, Mumps, Infectious Mononucleosis, Adenovirus Herpes Zoster, Cytomegalovirus), fungi (rare Histoplasma), protozoa (acantamoeba), from conjunctivitis, orbital cellulitis.
  - idiopathic.
  - autoimmune in: Sarcoidosis, Syrogren, Wegener.
  - Lymphoproliferative: Lymphoma, Adenocarcinoma [1].

Acute Dacryodenitis

- It is primary inflammation of the lacrimal gland, or secondary to local or systemic causes in: conjunctivitis (gonococcus, staphylococcus), orbital cellulitis, trauma, facial erysipelas.
- Symptoms
  - Moderate intestinal pain, accentuated by pressure.
  - Excess lacrimal secretion
- Signs
  - Edema, erythema in the supero-external region of the superior eyelid.
  - recumbent deformity of the upper eyelid.
  - if the orbital lobe is affected—painful proptosis, with limitation of eye movements.
  - pseudoptosis.
  - lymphadenopathy
- Treatment
  - Systemic: antibiotic, anti-inflammatory, analgezic.
  - Local heat.
  - Surgery with incision and drainage.

Chronic Dacryoadenitis

- It is accompanied by hypertrophy of the lacrimal gland and may be the sequel of an acute dacryoadenitis or may be associated with chronic inflammation of the conjunctiva in a systemic disease: TB, syphilis, sarcoidosis.
  - Clinic—eyelid edema, associated with ptosis, with downward displacement of the eyeball.
  - Treatment—of causing infecitons.

Mikulicz Syndrome

- It is the bilateral, symmetrical enlargement of the lacrimal and salivary glands in systemic diseases: leukemia, lymphosarcoma, Hodgkin, sarcoidosis, TB.

Infectious-Inflammatory Diseases of the Tear Ducts [2, 3]

Canalicular Obstruction and Canaliculitis

- It is—unsupervised—obstructive and—survived canaculitis and is produced:
  - Exogenous through: viral infections (HZV, HSV, trachoma), radiation, burns, fuorouracil, tumors, idiopathic.
  - Endogenous though: wegener, sarcoidosis, sjogren, pemphigoid.
- Clinic—Intermittent or constant lacrimation.
- Treatment
  - Partial canalicular obstruction requires partial intubation.
  - Total obstruction requires a dacryocystorhinostomy canal and/or a Jones tube depending on the length of the canalicular obstruction.

Obstruction of the Lacrimonasal Canal

- It is evident by the limitation of the lacrimal probe, with the distension of the sac during irrigation and reflux through the superior canaliculi.
- NLC obstruction etiology is: idiopathic and secondary in naso-orbital trauma, granulomatosis, Wegener, inflammation of a nasopharyngeal tumor.

Dacryocystitis

- Acute or chronic inflammation of the lacrimal sac associated with NLC obstruction that causes tears to accumulate in the sac where they stagnate and become bacterially superinfected; the most common germs are: Staphylococcus aureus, Streptococcus pneumonia, Pseudomonas, and Hemophilus (in children).
- Risk factors: deviated septum, rhinitis, sinusitis, nasal polyps.
- Dacryoscites has two clinical forms: congenital and acquired.

Congenital Dacryocystitis

Appears in newborns due to incomplete perforation of Hasner's membrane at birth, with NLC obstruction.

Congenital Dacryocystitis can evolve acutely or chronically [4].

Differential diagnosis of epiphora (lacrimation) in newborns: ophthalmia neonatorum, congenital glaucoma, trichiasis, entropion, ectropion.

Chronic Congenital Dacryositis [2, 4]

It is present in newborns, in children with NLC obstruction, with an incidence of 5–10%.

- Clinic
  - Persistent lacrimation in newborns in their first months.
  - Conjunctivitis refractory to treatment.
- Complications: Conjunctivits, exematation of the eyelid, acute dacryocystitis, chronic, lacrimal sac mucocele, sac fistula abscess.
- Treatment [5, 6]
  - Ocular hygiene
  - Massage of the lacrimal sac 5′ repeated four times a day.
  - Treatment of chronic congenital dacryocystitis according to age…

    0–3 months: Sac massage.
    3–6 months: Survey.
    6–9 months: Survey.
    6–12 months: Survey under general anesthesia.
    4–5 years: Endonasal Dacryocystorhinostomy
- Survey of the lacrimal ducts with the Bowmann probe 000–00 with a horizontal, vertical, horizontal route to the medial bone wall, then the probe is directed downward and vertically towards the first molar.

  - Washing the tear ducts with physiological serum or antibiotic.
  - If the child swallows the liquid, the survey has restored the permeability of the tear ducts.
- Surgical treatment—Dacryocystorhinostomy—DCR if conservative treatment is ineffective with endoscopic DCR.

Acute Congenital Dacryocystitis

It is the infectious inflammatory process of the lacrimal sac with NLC obstruction, suddenly installed in a newborn who presents epiphora at birth; the sac infection is saphylococcus [7, 8].

- Clinic—newborn with chronic dacryocystitis suddenly presents with…
  - inflammatory phenomena located at the level of the lacrimal sac on the inner wall of the nose with edema, redness, local warmth.
  - altered general condition with fever, chills.
  - secretion under pressure on the lacrimal sac.
  - can be triggered by an acute respiratory infection.
- Treatment—systemic antibiotic according to age.

Adult Dacryocystitis

Chronic Adult Dacryocystitis [1, 9]

- It is present in adults 40–60 years old, more frequent in women, in conditions of poor hygiene.
- Bacterial infection of the lacrimal sac with staphylococcus, pneumococcus, pseudomonas, pyocyanic, rarely TB, syphilis, leprosy, is caused by the saprophytic flora through the stagnation of tears in the sac in NLC obstructions or by superinfection from conjunctivitis, orbital cellulitis, and paranasal sinuses.

Clinic—differential diagnosis (Table 3.1)

- Initially accentuated chronic lacrimation, in the cold, wind, light, after which, after a long period (months, years), it becomes a purulent secretion, which can be discharged through the lacrimal points, with pressure on the sac.
- Hypertrophied lacrimal sac without inflammatory phenomena.
- NCL obstruction.

The presence of a chronic dacryocystitis in patients who require intraocular surgery, obligates the extirpation of the sac, DCR.

Table 3.1 Differential diagnosis in dacriocystitis

Symptoms	Chronic dacryocystitis	Acute dacryocystitis	Mucocele
Clinic	• Epiphora	• Brutal debut • Eyelid edema • Preauricular adenopathy	• Soft, painless swelling
Pain	• On palpation, feeling of pressure	+++	–
Reflux	–	Purulent	• Purulent or Mucous
General signs	–	+++	–
Clinical signs	• Catarrhal	• Suppuration	• Accumulation of tears in the sac and superinfection, with impossibility of evacuation with digital pressure due to double obstruction of the NCL and canaliculi

Surgical treatment

- **Dacryocystectomy**—Extirpated from the sac indicated for children under 4 years old or hardened people, the elderly, chronic infections of the sac (TB, syphilis), mycoses, tumors, atrophic rhinitis.
- **Dacryocystorhinostomy—DCR**—For the restoration of NCL permeability through direct anastomosis between the sac mucosa and the classic nasal mucosa through an external approach or endoscopy through an endonasal approach.
- **Advantages of Endonasal DCR**: does not require skin incision, less aggressive procedure with reduced bleeding, short duration.
- **Disadvantages of Endonasal DCR**: the success rate is smaller, it requires the ENT/ophthalmologist team and is more expensive.

Acute Dacryocystitis in Adults

- It represents the aggravation of a chronic dacryocystitis, accompanied by acute peridacryocystitis through infectious involvement of old age with bacteria (beta hemolytic streptococcus, staphylococcus, pseudomonas, escherichia), and fungi (candida).
- Clinic [10]
  - Pulsating pain in the internal angle associated with acute inflammatory phenomena in the region of the sac with **Peridacryocystitis** due to the extension of the preauricular adenopathy infection.
  - Preauricular Adenopathy
  - Abscess of the sac with its fissure and external fistula.
- Treatment
  - Local

    Decongestant cold spray (Rivanol).
    Antibiotic: Tobramicin, ciprofloxacin, netacin six times per day.
  - Systemic: Antibiotic—Augmentin, Cefalexin, Moxifloxacin.
  - In the lacrimal abscess—incision and drainage of the sac.
  - After the inflammation subsides, classical or endoscopic DCR.

Lacrimal Secretion Disorders

Corneal Dryness

Corneal dryness is NOT a clinical entity, it is a complex symptom secondary to a tear film deficiency or abnormalities [11, 12].

Advanced age and female sex are the most important risk factors for dry eye syndrome.

The tear film covers the corneal epithelium and the conjunctiva and is made up of three layers which, from the outside to the inside, are…

- **The lipid layer** released by the Meibomian glands ensures the stability of the tear film and reduces the evaporation of the aqueous layer.
- **The aqueous layer** secreted by the lacrimal gland and the Kraus and Wolfring glands helps to supply Oxygen to the corneal epithelium.
  - Deficiency of the aqueous layer in keratoconjunctivitis sicca is the most common cause of primary or secondary Sjogren's syndrome.
  - Postmenopausal women have a regrowth of this layer.
  - Mucous—internal layer is secreted by Goblet's conjunctival cells, Henle's crypts, Manz's glands. It is affected in Stevens-Johnson syndrome.

The tear film has the role of protecting the cornea and conjunctiva, provides oxygen to the corneal epithelium, washes the corneal surface of irritants, prevents possible infection due to the presence of bacterial germs, facilitates the movements of the eyelid above the eyeball.

Diagnostic Tests that allow the objectification of the presence of lacrimal dryness and the evaluation of the effects on the ocular surface.

Schirmer Test—measures the formation rate of the tear film using a 5 × 35 mm filter paper. 5 mm filter paper tape, in the shape of a crochet, placed in the bottom of the bag on the palpebral margin between the middle third and outer 2/3 of the lower eyelid, paper withdrawn after 5 min; the area of paper soaked with tears is appreciated.

Normal = impregnation >15 mm.

Corneal dryness <5 mm.

Tear Film Break Up Time (BUT)

- Physiological test that identifies the stability of the corneal film. A drop of fluorescein in the bottom of the lower sac, the patient blinks a few times, stops, the interval from the last blink to the appearance of signs of tearing of the lacrimal film is measured.
- Biomicroscopic exam
- Indicates the mucinous component of tears.

Normal = 10–35 s.

Unstable Lacrimal Film <10 s.

Staining with pink bengal 1% has an affinity for dead epithelial cells.

- Used for the diagnosis of medium forms of keratoconjunctivitis sicca.
- It shows very precisely the area of corneal or conjunctival epithelium that causes dry eye syndrome.

Green lissamine test—similar to pink bengal, but does not cause eye irritation.

Tear IgE dosage—the tears are collected on a filter paper (as with Schirmer); the increase of IgE shows allergy.

Electrophoresis of tear proteins—the increase in proteins suspects an inflammatory process.

Conjunctival or lacrimal gland biopsy—guides the diagnosis in the context of general symptoms (Gougerot Sjogren syndrome).

Complete immunological balance is necessary in autoimmune diseases.

- **Dry eye syndrome is a multifactorial condition of the ocular surface characterized by complex symptoms, followed by scarring sequelae produced by tear film deficiency.**
  - The most frequent in women over 65, with a frequency of 15%.
  - It is accompanied by an increase in tear osmolarity and inflammation of the ocular surface—it is a complex symptom that follows quantitative and qualitative lacrimal dysfunction.
- Variable symptoms
  - Sensation of dryness, stinging, foreign body, or burning.
  - Ocular pain.
  - Frequent blinking.
  - Photophobia.
  - Pruritus.
  - Secondary cleaning of the ocular surface, alteration of the quality of the tear film, its decrease or absence with intermittent red eye and decrease in Visual Acuity.
  - Constant symptomatology with variable rhythm depending on the presence of triggering factors: visual excess, presence of polluting factors (tobacco, hot, humid climate).
- Clinically, most frequently there are NO objective changes, although there are subjective symptoms present, but there may be…
  - Diffuse conjunctival hyperemia sometimes associated with hyperemia of the free edge of the eyelids and foamy secretory deposits.
  - Abnormally concave, irregular, fine or absent lacrimal meniscus.
  - Corneal lesions revealed by fluorescein staining…

Punctate Keratitis and inferior superficial mucous plaques.

Filamentous Keratitis with mucolipid lacrimal secretion that remains acrostic on the corneal surface.
Corneal ulceration in corneal cases.

- Research on the existence of dry mouth.
- Tear film rupture time <10 s.
- Conjunctivitis corneo staining with Benegal pink.
- Schirmer Test <6 mm

Causes of Filamentous Keratitis

- Ocular: Keratoconjunctivitis sicca, upper limbic keratoconjunctivitis, prolonged eye dressing, recurrent corneal erosion, keratitis.
- Systemic: essential blepharospasm, brain stem stroke.

Dry eye syndrome with keratoconjunctivitis sicca is produced by [5]

- Insufficient lacrimal secretion in Sjogren's syndrome.
  - Primary—Autoimmune inflammatory disease with chronic evolution in women 40–50 years old with keratoconjunctivitis sicca and xerophthalmia.
  - Secondary—Associated with an autoimmune disease: Rheumatoid arthritis, juvenile idiopathic arthritis, SLE, psoriasis, multiple sclerosis, dermatomyositis, polychondritis, Hasimoto thyroiditis or infiltrative in: sarcoidosis, hyperthyroidism, lymphoma, hemochromatosis, amyloidosis.
- **Non-Sjogren's dry eye**—with sica keratoconjunctivitis in the absence of autoimmune changes from Sjogren's can be…
  - Primarily through: age-related primitive ocular dryness, familial dysautonomia, congenital alacrimia.
  - Secondarily through…

    Infiltration—sarcoidosis, amyloidosis, lymphoma.
    Obstruction of the tear ducts—trachoma, ocular pemphigoid, burns, post-radiation fibrosis.
    Reflex hyposecretion; neurotrophic keratitis, HSV keratitis, HZV, LC, paralysis VII.
    Toxic drugs: atropine, antidepressants, neuroleptics, morphine, antihistamines, antiretrovirals.
- **Evaporative dry eye syndrome** due to excessive evaporation of water from the ocular surface exposed to the environment, in the presence of normal lacrimal secretion.
  - Intrinsic Causes

Meibomius gland dysfunction—posterior blepharitis is the most common cause of evaporative dry eye with a deficiency of the lipid layer of the tear film.
Palpebral dynamics disorders in proptosis, strong myopia, and craniostenosis.
Decreased blink rate.
Medicines—systemic retinoids.

– Extrinsic Causes

Vitamin A deficiency with watery lacrimal deficiency.
Toxic agents for the ocular surface—preservatives—benzalkonium chloride, topical anesthetics.
Contact lenses.

- **Conserved Lacrimal Secretion**

– Excess Lacrimal Evaporation

Palpebral inocclusion, VII paralysis, posttraumatic, scars, tumors.
Qualitative and/or quantitative defect of the lipid layer of the tear film: blepharitis, eye drops with preservatives.
Spreading defect of the tear film.
Eyelid changes: entropion, ectropion, trachoma, burn sequelae.
Corneal anomalies: scars, pterygium, LC.

Etiological diagnosis of dry eye is necessary. The treatment aims at: improving symptoms, normalizing the ocular surface, preventing corneal damage.

Dry eye syndrome is a chronic, progressive condition with limited possibilities of complete healing, sometimes.

- Measures to preserve the tear film by: heating the temperature in the room, using the room humidifier, protective glasses, in severe forms of keratoconjunctivitis sica—partial tarsoraphia.
- Medical treatment [13]

– Local
– Artificial tears with frequency of administration depending on the severity of the syndrome; in severe forms hourly, in medium ones 4–6 months times a day.
– Topical solutions containing long-lasting mucoadhesives; viscosity-increasing agents: polycarbiphil, dextran, polymer-based substances, polyvinyl pyrrolidone, L carnitine, betadine, and autologous serum.
– Tear gels: high molecular weight polymers of acrylic acid and sodium hyaluronate 0.1%; they persist at the bottom of the bag for several hours.
– Ointments based on lanolin, mineral oils.
– Mucolytic eye drops: mucosolvan, 5% acetylcysteine excess mucus and for decreasing tear viscosity.
– Topical retinoids.
– Ciclosporin 0.05–0.1% reduces inflammation.

Systemic—NSAIDs and corticosteroids to reduce inflammation.
Topical and systemic antibiotic treatment: tetracycline, doxycycline, azithromycin.
Oral bromhexine 32 mg/day for the effect of stimulating tear secretion.

- Surgical treatment—Partial tarsorrhaphy, amniotic membrane graft.
- Treatment with soft contact lenses used simultaneously with artificial tears in single doses.
- Decreased tear drainage through…
  - Treatment of posterior blepharitis.
  - Methods of lacrimal stimulation.
  - Correction of changes in the position of the eyelids.
- Ways to preserve tears—Tarsoraphia.
- Patients with dry eye syndrome are at increased risk of eye infections, therefore they must be considered in cataract surgery.

Lacrimation

- Lacrimation is a frequent, uncomfortable symptom produced by excess tears.
- Excess tears are produced by: hyperlacrimation or epiphora.

Hyperlarimation is…

- ***Primary***—rarely, in cysts, lacrimal gland tumors or through parasympathomimetics.
- ***Reflexive***, through stimulation of the sensory branches of NC V by irritation of the cornea and conjunctiva in the infectious-inflammatory pathology of the anterior pole: conjunctivitis, keratitis, episcleritis, iridocyclitis, acute glaucoma, endophthalmitis, orbital cellulitis, palpebral infection (internal organitis, meibomitis, trichiasis, entropion).
- ***Central***—physical lacrimation—emotional, hysterical.

Epiphora is…

- **Physiological**—lacrimal pump defects due to eyelid laxity or orbicularis muscle weakness.
- **Mechanics**—through obstruction in the drainage of tears at the level of…
  - Lacrimal points: eversion in the elderly, in conjunctivitis, chronic blepharitis, entropion, post-burn or post-infectious scars, pilocarpine, idoxuridine can produce punctal stenosis.
  - Congenital or acquired post-traumatic obstructed canaliculi, canaliculitis.
  - Lacrimal sac—dacryocystitis (TB, syphilis), tumors, sac atony.
  - Nasolacrimal canal: congenital with NCL imperforation or acquired in post-traumatic, post-inflammatory NCL obstruction, tumors.

The clinical evaluation of lacrimation is done by…

- **The Jones 1 test** allows the differentiation of an excessive secretion through partial obstruction of the tear ducts from primary hypersecretion. A drop of 2% fluorescein solution is instilled into the conjunctival sac; after 5 min, a stick with 4% cocaine is positioned at the opening of the nasolacrimal duct.
  - If the fluorescein solution reaches the stick in 1 min, then the excretory system is intact, the cause of lacrimation being primary hypersecretion = the test is positive.
  - If the fluorescein solution does not reach the outside, there is a partial obstruction of the tear ducts.
- **The Jones 2 test** helps to identify the level of partial obstruction.
  - Topical anesthesia with xylin 4% is instilled in the conjunctival sac, the nasolacrimal system is irrigated with saline solution, the patient being positioned head down at 45° so that the saline solution comes out of the nose and not inside the formix.
  - Results

    A positive result indicates a partial obstruction of the nasolacrimal duct that can be treated by dacryocystorhinostomy.
    A negative result indicates a partial obstruction in the upper drainage system (point, canaliculi or common canaliculi) or a defect of the lacrimal pump.
- **Fluorescein Disappearance Test**
  - The instillation of 2% fluorescein in the bottom of the lower sac, the color intensity after 5 min is graded on a scale of 0–4: a normal secretion must be between 0–1; if this gradation is exceeded, insufficient evacuation is demonstrated.
  - This test complements the Jones tests.

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Chapter 4
Ophthalmological Pathology of the Eye: Eyelids

Marieta Dumitrache and Rodica Lascu

Abstract **Infectious-inflammatory diseases of the eyelids** affect the free edge of the eyelids—blepharitis and palpebral glands—internal stye, external stye and chalazion. **Blepharitis** is the chronic, recurrent inflammation of the free edge of the eyelid and can be anterior, around the cilia (staphylococcal, seborrheic, mixed) and posterior, affecting the orifices of the Meibomian glands and mixed. **Stye** is the acute staphylococcal infection of the sebaceous gland of Zeis, internal stye and Meibomius (internal stye), conditions that require local, decongestive treatment, if necessary the opening of the abscess with a laser. **Chalazion** is the chronic non-infectious inflammation of the Meibomian gland that requires surgical treatment if necessary. At the level of the skin of the eyelids, there may be: edema, ecchymosis, bacterial infections (erysipelas, impetigo, viral infections HSV, HZV), dermatological diseases (contact dermatitis, atopic dermatitis, eczema, rosacea acne). **The positional abnormalities of the eyelids** are: congenital spastic, cicatricial, involutive **entropion**, and cicatricial, paralytic, senile **ectropion**. At the level of the eyelids, palpebral motility disorders may be present with narrowing of the palpebral fissure in **ptosis and blepharospasm** or widening of the palpebral fissure in **lagophthalmos and palpebral retraction. Eyelid tumors** are rare, and can be benign (papilloma, xanthelasma, hemangioma, neurofibroma), precancerous (actinic keratosis) or malignant (squamous, basal and squamous cell, melanoma, adenocalciroma).

Keywords Anterior blepharitis · Posterior blepharitis (Meibomitis) · External Internal stye · Cutaneous erysipelas · Impetigo · Eyelid eczema · Contact dermatitis · Entropion · Ectropion · Eyelid ptosis · Blepharospasm Lagophthalmos · Eyelid retraction · Eyelid tumors

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Eyelids are two musculo-cutaneous formations located in front of the eyeball that delimits the palpebral slit and provides protection to the eye from external trauma and excessive light. The eyelids contribute to the formation and distribution of the tear film and have a role of the pump in the drainage of tears through the lacrimal pathways.

Infectious-Inflammatory Diseases of the Eyelids

- Infectious inflammatory diseases of the eyelids can affect palpebral (blepharitis), palpebral glands, skin and subcutaneous tissue.
  - Blepharitis-infectious inflammatory process at the level of the **palpebral margin—anterior, posterior blepharitis**
  - **Infections of the glands in the eyelid: external, internal orgelet, salazion**
  - **Bacterial and viral infections of the skin of the eyelids**

BLEPHARITIS is chronic, recurrent inflammation of the palpebral free edge.

It is found with a prevalence of 37–47% among patients who present at the offices ophthalmology. Etiology can be bacterial, seborrheic, parasitic, atopic, allergic.

The etiopathogenesis of blepharitis is incompletely elucidated, but there are favorable factors: uncorrected refractive defects, allergy, pollution, diabetes, corneal dryness syndrome, cold, cosmetics, hormonal factors, immunodeficiency, seborrheic dermatitis, acne rosacea [1].

Acute blepharitis can occur through bacterial infection (Staphylococcus aureus), viral (HSV), atopic blepharodermatitis, seasonal allergic blepharoconjunctivitis.

Chronic bleraphitis—is chronic infectious or non-infectious inflammation.

Blepharitis is…

- Anterior around the cilia: staphylococcal, seborrheic, mixed
- Posterior affecting the orifices of the meibomian glands
- Mixed

Anterior Blepharitis [2]

- ***Staphylococcal blepharitis***
  - clinically manifested by conjunctival hyperemia at the level of the free edge of the eyelids in the anterior portion with the presence of scuffs at the base cilia, and sometimes the presence of cicatricial lesions crusts, madarosis
  - may be complicated by: superficial punctate keratitis, marginal keratitis, instability of the tear film
  - complications: chronic conjunctivitis, superficial punctate keratitis inferior, marginal keratitis (corticoids)

- Treatment-eye hygiene

  hot compresses and massage
  antibiotic pomade
  steroid-ointment
  systemic-tetracycline

- ***Seborrheic-scallop blepharitis***—is a disorder of the Zeiss glands and is associates with seborrheic dermatitis of the eyebrows, scalp and region nasolabial;
  - pityrosporum ovale infections with irritant action on bacterial lipase
  - clinically the presence of scallops on the free edge of the eyelid that they peel off easily and leave no ulcers or bleeding areas
  - treatment:

    similar to staphylococcal blepharitis
    removing crusts with a dry swab, after applying a tampon soak with warm water for 2–3 min on the edge of the eyelid

- ***Ulcerative blepharitis***—Ulcerative blepharitis is more serious, causes many complications and is more difficult to treat and cure.
  - staphylococcal infection associated with seborrhea with damage especially to upper eyelid
  - clinically at the base of the eyelashes are yellowish crusts, difficult to remove (after removal remains a bleeding surface)
  - complications: chronic conjunctivitis, keratitis, marginal infiltrates, corneal dezepithelizations, corneal neovascularization
  - Treatment [3, 4]:

    correction of refractive defects
    eye hygiene
    broad-spectrum antibiotics drops, ointment 3/day

  - if there is no response to local treatment systemic antibiotic treatment is necessary for 7–10 days

Posterior Blepharitis

- is dysfunction of the meibonius glands with obstruction of the excretory ducts diseases of the gland through the sebum plug, followed by inflammation of the glands Meibomius and dysfunction of the tear film.
- clinical
  - the free edge of the eyelid thickened and hyperemic, with vascular telangiectasias
  - swollen meibomius glands blocked by sebum at palpebral pressure sebum is expressed

- complications: Salazion, recurrent orgelet, Sica keratoconjunctivitis, lower epithelial keratitis
- local treatment
  - topical: tobradex (drops, ointment), azithromycin (sol. 1%)
  - identical as in previous blepharitis: antibiotic ointment: bacitracin, erythromycin
  - corticosteroids-methylprednisolone 1% 2/day
- systemic treatment [5, 6]
  - tetracycline 250 mg 4/day, 1 week, then 2/day 6–12 weeks
  - doxycycline 100 mg 2/day 1 week, then 100 mg/day-6–12 weeks
  - minocilin 100 mg/day 6–12 weeks
  - azithromycin 500 mg/day—1 week
  - metromidazole
  - ciclosporin-Restasis 0.05%—3 months
  - tacrolimus 0.03% solution, 0.01% ointment

Angular Blepharitis

- is infection with Moraxela lacunata or Golden Staphylococcus clinically-red, macerated skin in the internal Cantus
- treatment
  - pomade with rifampicin
  - LIPOFLOW (intense pulse light) and/or intraductal treatment in the Meibomus gland or mechanical with probing of the gland

Diseases of the Palpebral Glands [7]

- **Orjelet (hordeolum)**
- It is an abscess by acute, suppurative staphylococcal infection of the sebaceous Zeiss glands (external orjelet) and meibomius (internal orjelet) that occurs in isolation or secondary to a blepharitis.
- Subjective symptomatology includes feeling of embarrassment, heat, twitching in the eyelids.
- Objectively there is an inflammatory edema of the eyelids, which after 2–3 days it centers on a yellow spot that grows rapidly, turning into a pimple that opens spontaneously, draining a yellow pus. It can puncture the collection, preferably with the Cauter, then letting it drain spontaneously.
- The upper eyelid is affected more frequently

- Preauricular ganglia are always affected
- Conjunctivitis is commonly associated
- Evolution: after the discharge of pus, the pains alleviate and disappear, the palpebral edema regresses and the ulceration cicatrizes. Sometimes the infection can propagate to other follicles, producing serial orjeletes.

Treatment
- warm, dry compresses, Cilia epilation
- analgesics, NSAIDs
- laser abscess opening
- ophthalmic ointment

Internal Orjelet—acute staphylococcal infection of the meibomius gland
Symptoms and clinical signs similar to the external orjelet, but more intense

Treatment
- local
- warm compresses
- Erythromycin, Tobradex
- if the lesion is prolonged, local and systemic antibiotic

Salazion-meibomian or Tarsal Cyst (Fig. 4.1)

- chronic, non-infectious lipo-granulomatous inflammation of the Meibomius glands, more common in uncorrected refractive vices, caused by blockage of the glandular orifices, stagnation of sebaceous secretions and accumulation of meibomian secretions.
- More common condition in adults (androgen hormones increase viscosity sebum), in the upper eyelid, Salazion may be associated with chronic blepharitis, rosacea, seborrheic dermatitis.
- Clinically-painless tarsal Node located on the external side of the eyelid, sometimes on the conjunctival face with variable evolution from spontaneous resorption until chronicling.

Fig. 4.1 Salazion

- Treatment
  - surveillance for possible spontaneous healing in small salazions
  - corticoid antibiotic pomade
  - intralesional injection 0.5 ml with steroids, triamcinolone acetate 10 or 40 mg/ml
  - surgical treatment—vertical incision at conjunctiva/horizontal, at skin, curettage of the contents, cauterization, antibiotic ointment.

Diseases of the Skin of the Eyelids

Oedema, Ecchymosis, Discolouration

- **Palpebral edema**
  - inflammatory

    infections of the eyelids: bacterial (abscess, cellulitis, orjelet), viral (area shingles, herpes, chicken pox, measles), fungal, parasitic
    infections of the eyeball: severe uveitis, endophthalmitis, conjunctivitis purulent, panophthalmia
- **Orbital cellulite**
  - thrombosis of the cavernous sinus
  - exophthalmia
  - allergic: acute angioneurotic oedema, insect stings/bites
  - systemic cause: acute and chronic nephritis, hypoproteinemia, myxedema, thyrotoxicosis
  - **urgency in palpebral edema is present when edema is associated with: changes in vision, diplopia, ophthalmoplegia, sinus thrombosis cavernous, endophthalmitis**
- Edema can be acute or chronic; it can affect one or both eyelids; it can be slightly fluffy in appearance, or it can be so pronounced that it covers palpebral cleft, requiring a spreader to separate the eyelids; be transient, appearing only at a certain time of the day, or permanent.
- **Palpebral ecchymosis**—the ecchymosis can only be located at the level of eyelid or may be associated with subconjunctival hemorrhage with or without laceration of the eyeball. Although they have a worrying appearance, they do not affect vision and usually disappear without treatment after 7–10 days. Sometimes bruising may be a superficial sign of deep ailments (basic fracture of skull, blood dyscrasias, neuroblastoma, traumatic optic neuropathy)
- **Changes in eyelid color**—the color of the eyelids is similar with that of the face. Sometimes temporary color changes occur.

Bacterial Infections of the Eyelids

Palpebral Phlegmon

- Diseases with onset in the dermis, by infection with hemolytic Golden Staphylococcus,
- Hemophilus in children
- Clinically-marked edema of the eyelid

Palpebral Abscess

Diffuse inflammation with edema and important congestion of the eyelid that can close the palpebral slit.

Treatment
- local compresses with rivanol
- systemic-immediately with a gram-positive effect: penicillin, cephalosporins, Macrolides, Quinolone
- in methicillin-resistant Staphylococcus-clindamycin, Trimetropin, vancomycin
- surgical-incision and drainage

Necrotizing Fasciitis

- Serious infection of the subcutaneous soft tissue by streptococcal infection pyogenic or Golden staphylococcus, which causes thrombosis and necrosis, with eyelid black, necrotic
- IV treatment.
  - broad-spectrum antibiotic i.v.
  - debridement of necrotic tissue

Diffuse Bacterial Infections [1]

Impetigo

Contagious skin infection with Golden Staphylococcus, pyogenic Streptococcus.
Clinically-blisters that if burst leave an ulcerated surface and yellowish crusts.

Treatment
- local-fusidic acid ointment, baneocin, rifampicin pomade
- systemic-NSAIDs, erythromycin

Erysipelas

- Superficial, edematous skin infection with delineated edges, infection with pyogenic Streptococcus.
- Clinical
  - sudden onset with fever, shiver, altered general condition
  - local-indurated cutaneous area frequently located in the internal angle with erythematous plaque
- Treatment
  - local-rivanol compression, touches with iodine
  - systemic-penicillin G 10–15 days, erythromycin, Pristamycin

Viral Palpebral Infections

- **Herpes simplex virus**
  - Primary HSV infection of medium intensity, with painful embarrassment, itching and redness.
  - Clinically-seropurulent vesicles on the eyelid that break and crusts appear.
  - Complications-ulcerative blepharitis, follicular conjunctivitis, keratitis dotted or dendritic
- Treatment
  - systemic—Zovirax 400 mg × 5 g, famciclovir—500 mg/day, valaciclovir 1 g/day
  - local-Acyclovir

Ophthalmic Shingles

- Increased incidence and severity with age
- Clinical
  - unilateral painful cutaneous maculopapulosa rash, followed by ulcers and crusts localized in the territory of the ophthalmic branch of the NCV
  - Various corneal damage: punctiform corneal epithelial infiltrates, corneal hypoesthesia, disciform keratitis

    corneal lesions do not succumb to antivirals, but respond to corticoids damage to the anterior uvea primary or secondary to keratitis

- Complications:
  - palpebral: trichiasis, madarosis, ptosis, entropion, ectropion
  - anterior pole: follicular conjunctivitis, episcleritis, scleritis, keratitis, anterior uveitis
  - corneal hypoesthesia
- Treatment
  - local-antiviral-Acyclovir cream
  - systemic

    Acyclovir, famiciclovir, valaciclovir
    treatment of NC V neuralgia with tricyclic antidepressants (amitriptyline, Doxepin, Gabapentin)

Dermatological Diseases of the Eyelids

Contact Dermatitis

It is mediated by a type IV allergic hypersensitivity reaction in the presence of possible treatment of allergens: pollen, cream, cosmetics, spray, ophthalmic solutions.

Treatment
- Local
- tacrolimus (first line therapy)
- steroids (hydrocortisone, fluorometalon)
- antibiotic ointment (erythromycin, bacitracin)
- Oral antihistamines

Atopic dermatitis—Chronic relapsing disease (patients may have multiple impairments of cell-mediated immunity)

Clinical
- pruritus, oedema, erythema, fissures, flaking
- it can be complicated by infection or contact dermatitis

Treatment
- systemic antihistamines
- Local
  - Tacrolimus (Protopic) and Pimecrolimus (Elidel) in refractory cases
  - short-term low-dose corticoids
  - moisturizing creams
  - antibiotics in superinfections

Dry, Wet Eczema

By skin contact with allergens: cosmetics, microbes, Mycoses, medicine.

Treatment
- relieve itching
- antiseptic compresses
- chronic forms—galvanized paste, cortisone ointment
- antiallergic

Rosacea

Chronic inflammation of the face and eyelids

Clinical
- skin manifestations 20%—acne, telangiectasis of the skin in the region Malar (red), persistent facial erythema
- eye damage—recurrent blepharitis, conjunctivitis, hordeolum, panus

Treatment
- local dermatological
- systemic (doxycycline 100 mg or Minocilin 500 mg, 3 weeks or Tetracycline alternative with erythromycin)
- Ocular
  - local-eyelid hygiene
  - topically-azithromycin, azaleic acid, clindamycin, metronidazole ointment (0.75%) in refractory forms
  - steroids when needed

Moll cyst—apocrine hydrocystoma-small round lesion at the edge of the eyelid.

Ecrin hydrocystoma—similar lesion, but not located on the edge of the eyelid.

Zeiss cyst—small round lesion, on the edge of the eyelid containing sebaceous secretion

Sebaceous cyst—lesion similar to the Zeiss cyst but localized at the internal angle.

Inclusion cyst—mobile subcutaneous lesions, more often in the upper eyelid, secondary to trauma or palpebral surgery

Millium bunch of tiny cysts originating from pilosebaca follicles

Diseases of Cilia

Trichiasis

Represents the orientation of the posterior Cilia with respect to normal, idiopathic or secondary in: chronic anterior blepharitis, ophthalmic area, trachoma.

Treatment-epilation, electrolysis, cryotherapy, lamellar discision and cryotherapy on the anterior lamella

Distichiasis

- Congenital
  - AD, the presence of a second row of short and fine Cilia, often directed posterior with emergence behind the orifices of the meibomius glands
  - treatment—lamellar palpebral discision and cryotherapy of the posterior lamella
- Acquired metaplastic Cilia by fibrous conjunctivitis associated with bullous pathology, chemical burns—treatment-epilation, lamellar discision and posterior cryotherapy

Ptosis of cilia—idiopathic or secondary in dermato-chalazis, old facial paralysis

Madaroza

Is the partial or total disappearance of cilia of local cause (anterior blepharitis chronic, tumors, burns), iatrogenic (radiotherapy, cryotherapy), skin disorders (area Ophthalmic shingles, atopic dermatitis), system diseases (syphilis, SLE, Ehler Danlos) drugs (cytotoxic, anticoagulants), congenital (CIL agenesis, palpebral coloboma).

Poliosis

Is premature bleaching of hair at the level of the cilia of local cause (blepharitis anterior, sympathetic ophthalmia), systemic (Vogt Koyanagi Harada syndrome, albinism, tuberous sclerosis), drugs—antipaludic.

Hypertrichosis

It is represented by an excessive number (polytrichosis) and/or excessively long cil (tricomegaly) of congenital cause or toxicity of drugs (prostaglandins, cyclosporin, phenytoin cortisone).

Molluscum Contagiosum

Epidermal infection by epidermal molluscum virus, disseminated by contact directly or secretions.

Clinically—pale grayish umbilicate nodule at the edge of the eyelid

Complications

- follicular conjunctivitis, superficial panus, punctate keratitis
- tendency to dissemination in immunodeficiencies.

Anomalies of the Position of the Eyelids

Entropion [8]

Entropion is the Rolling of the edge of the eyelid inside and can be: entropion congenital and acquired entropion that can be spastic, senile, cicatricial, mechanical.

Congenital Entropion

It is very rare and may be associated with microphthalmia.

Spastic Entropion is produced by spasm of the orbicular in patients with chronic irritative corneal disorders, with prolonged ocular dressing, more common in elderly people.

Clinical-lacrimation, photophobia, painful red eyes

Causal treatment

- artificial tears, ointment, surgical treatment, toxin injection botulinum in the orbicular muscle
- 85% favorable prognosis with resolution of the cause

Cicatricial Entropion is produced by cicatricial retraction of the conjunctiva palpebral pain associated with Tarsus distortion in: trachoma, membranous conjunctivitis, chemical burns, pemphigus, Stevens Johnson syndrome.

Clinical-pain, lacrimation, photophobia, variable AV Corneo conjunctival damage.

Surgical treatment depending on etiology: resection skin, muscle + Tarsus

Senile Entropion (Involutive)

Affects the lower eyelid in older people by degenerative lesions diseases of the muscle fibers of the orbicular, laxity of pretarsal tissues.

Treatment of senile entropion is surgical.

Ectropion—consists of outward spoilage of the ciliary Margin [2].

- Congenital ectropion-rare
- Ectropion won
  - the eversated conjunctiva takes on a pavimentous appearance, leading to conjunctival epidermization
  - the lacrimal point Evers, leading to chronic lacrimation

Clinical forms: spastic, cicatricial, paralytic, senile, inflammatory:

- *Spastic ectropion*: occurs following an acute palpebral disorder.
- *Cicatricial ectropion*: occurs following retractile scarring of eyelids (after burns, trauma, tumors); treatment is surgical, restoration of the eyelid by plasty.
- *Paralytic ectropion*: interests the lower eyelid; occurs after paresis of facial; treatment is surgical.
- *Senile ectropion:* it is bilateral and is due to tissue relaxation the lower eyelid elongates and Everses, over-infects, appearing blepharo-chronic conjunctivitis, which accentuates ectropion; treatment is surgical.
- *Inflammatory ectropion:* it is superinfected senile ectropion, when it occurs secondary inflammation of the conjunctiva of the eyelids, which accentuates the ectropion; treatment is etiological, and then surgical.

Palpebral Ptosis [7]

Palpebral ptosis is the more pronounced fall of the upper eyelid over the upper part of the cornea to more than 2 mm vertically.

Pseudoptosis can be given by causes:

- palpebral: palpebral oedema, hemangioma, Neurofibroma, Sturge Weber syndrome, chalazion, palpebral abscess
- eyeball-microphthalmia, atrophic globe, enophthalmia, anophthalmia
- orbit-orbit fracture

Classification of Ptosis

Neurogenic ptosis by innervation deficiency of the superior eyelid lifting muscle

- NC III paralysis: ptosis, adduction deficiency, uplift, eye twist that increases to looking down, mydriasis, accommodation paralysis

- Claude Bernard Horner syndrome: ptosis 1–2 mm, miosis with anisocoria accentuated in obscure, normal reaction to light and convergence, facial anhidrosis, slow pupillary dilation.
- Marcus Gunn syndrome—abnormal connection between the mandibular branch of NC V and the eyelid lift upper with: eyelid retraction, ptosis when muscles are stimulated pterygoids at mouth opening, mastication (mandibulo palpebral synkinesia)
- aberrant regeneration CN III—abnormal regeneration of NC III nerve fibers after paralysis acquired by CN III with: ptosis associated with abnormal movements of the upper eyelid with eye movements.

Myogenic ptosis by myopathy of the lifter

- congenital
- ocular myopathy
- blepharophimosis
- neuromyopathies in myasthenia
- aponeurotic by deficiency of the lifting aponeurosis
- mechanical in edema, scars

Congenital Ptosis

It accounts for 75–80% of all ptosis, is one-sided AD in 70%, forms bilateral, being generally asymmetric, is accompanied by deficiency of the riser and absence of palpebral fold

- affects both sexes equally and there may be several members of the same families with ptosis
- simple congenital ptosis is non-progressive, AV is normal or exists refractive defects (astigmatism), may accompany amblyopia
- complicated congenital ptosis may be associated with damage to other muscles extraocular, innervated by NC III (upper right), with abnormalities of other CN, congenital ptosis associated with cervical sympathetic impairment, or palpebral ptosis associated with palpebral abnormalities: epicanthus, blepharophimosis

Acquired ptosis depending on the cause is:

Neurogenic—by defect of innervation, in NC III paralysis, Horner syndrome, ophthalmoplegic migraine, multiple sclerosis.

Myogenic—in patients with Myasthenia Gravis, myotonic dystonia, ocular myopathy, oculopharyngeal and posttraumatic dystrophy:

- symptoms: ptosis, diplopia, strabismus
- medical treatment: anticholinesterase, steroids, azothioprine, cyclosporine

Aponeurotic—develops by aponeurotic defect in people with function normal muscle in: senile involution with ptosis and post-operative ptosis after cataract (rare), DR, blepharosalasis, dehiscence or aponeurotic desinsertion in trauma.

Mechanical—in tumors, eyelid edema, scarring in trachoma, pemphigoid.
Treatment of ptosis is surgical in:

- in severe congenital ptosis is indicated early surgery to prevent amblyopia (3–4 years) by:
  - Fasanella Servat technique for medium ptosis and good function of lifter
  - resection of the riser for moderate and severe forms of ptosis
  - Brow suspension in severe ptosis forms without lifting function with anchoring to the frontal muscles with broad fascia or non-absorbable thread
- acquired ptosis-treatment is indicated depending on the cause determinant of ptosis—in the neurogenic form conservative surgical treatment after 6 months of accident with procedures from congenital ptosis.

Palpebral Motility Disorders [2]

- Conditions that cause narrowing of the palpebral slit
  - Palpebral ptosisPalpebral ptosis
  - Blepharospasm
- conditions that cause enlargement of the palpebral slit
  - Lagophthalmia
  - Palpebral retraction

Palpebral Ptosis

Blepharospasm is the exaggerated spastic contraction of the isolated orbicular or component of a neurological syndrome, reflex or by facial irritation.

- *Reflex blepharospasm-irritation* of the sensitive branches of the NC occurs V, which are transmitted CN VII and may be ocular (infections, inflammation, trauma) or extraocular (ENT, dental, tumours)
- *Blepharospasm by irritation of NC VII* by abnormal muscle contraction in: epilepsy, neurosis, tumors, abscesses, brain hemorrhages, treatment is of the causal condition or facialization at the level of the Stylo-mastoid hole.
- *Benign essential blepharospasm*—with frequent blinking onset, associated with dystonic movements of the muscles of the face until the onset of uni spasm-bilateral.
  - Medical treatment (lorazepam, clonazepan), botulinum toxin, upper cervical ganglion

Paralysis of the orbicular is the consequence of paralysis of the facial and manifests itself by **Lagophthalmia** in which the upper eyelid descends by weight, the

lower one it departs from the globe with ectropion of the lacrimal point and permanent Epiphora.

- due to insufficient palpebral occlusion, the cornea dries up, ulcerates, superinfects and installs lagophthalmic keratitis
- causes of lagophthalmia
  - facial paralysis
  - mechanical: palpebral coloboma, palpebral scarring, enlarged simblefaron, entropion, proptosis, exophthalmos, ptosis overcorrection
  - Bell's palsy—acute unilateral facial palsy (damage to VII CN in facial canal) of viral, autoimmune cause manifested by the impossibility of symptoms of eye closure and lacrimation, preceded by auricular pain and mastoid damage
  - bilateral lagophthalmia of central cause in Moebius syndrome (paralysis congenital CN with V-VII impairment associated with VI paralysis), Melkerson-Rosenthal (peripheral facial diplegia, edema of the face, plicaturate tongue, trauma, brainstem glioma, Lyme disease, Guillaume Barrymore syndrome, sarcoidosis, myasthenia gravis

Palpebral retraction can be:

- isolated or associated congenital in: Down syndrome, Duane, hyperthyroidism
- acquired-thyroid ophthalmopathy, Horner's syndrome, encephalitis, disease cerebellar, coma, myasthenia, surgery (glaucoma orbitotomy), meningitis, tumours (sphenoid wing meningioma)
- Uni or bilateral palpebral retraction is manifested by the opening of more large palpebral slit.

Etiology of palpebral retraction: Cause

- the most common is: dysthyroid myopathy secondary to a sympathetic hyperactivity of the M muscle and dorsal midbrain lesion:
- sympathetic retraction of the eyelid with widening of the slit, mydriasis, exophthalmia, increased sweating, low temperature on the affected side
- cicatricial lesions in: infections, trauma, postoperative

Surgical treatment with posterior repositioning of the lifter together with the Muller muscle,

Eyelid Tumors [9]

Tumors of the eyelids interest the skin, supporting tissue, glands, vessels, nerves, muscles located in the eyelid.

Benign tumors: papilloma, xanthelasma, hemangioma, Neurofibroma, adenoma Sebaceous.

Precancerous tumors—actinic-solar keratosis, carcinoma in situ, Xeroderma Pigmentosum.

Malignant tumors—squamous carcinoma, basal cell carcinoma, melanoma Malignant, sebaceous gland adenocarcinoma

Benign Tumors

Papilloma is the most common benign tumor of the eyelids and presents itself in two forms:

- Squamous (grayish, present in the adult, stationary or slow-growing), pedicular located on the edge of the eyelid, requires simple excision
- Seborrheic keratosis in elderly people with brown lesions, with warty, friable, pigmented surface.

Xanthelasma

- yellowish placard, more common near the internal Cantus, present in women of middle age
- represents lipid deposit located in the dermis of the eyelid and can be associated with diabetes mellitus and elevated cholesterol levels.
- Treatment: excision of the tumor for aesthetic purposes, but relapse is common.

Pyogenic granuloma—Clinically rapidly growing bleeding rosette Mass, often the consequence trauma or infection of the eyelids.

Keratoacanthoma—Fast-growing node, containing a crater with spontaneous involution after a few months.

Melanocytic Nevus—papillomatous or flat lesion, variably pigmented which can be: intradermal, junctional, compound.

Hemangioma of the Eyelid

Capillary hhemangioma-is the most common congenital eyelid tumor. May be present at birth as a red spot on the eyelid and expand on forehead. Usually, lesions become prominent on the midline when the baby is crying. They have a typical evolution: they become manifest after the first month and continue to progress for another 6 months—1 year, after which they begin to regress up to 3 years. Little remains visible after 5 years.

- Treatment [9, 10]:
  - medical treatment consists of prednisone 2 mg/day, preferably in doses single and alternate days. Most regress significantly within 10 days, then the dose can be decreased.

- injection of the depot steroid in the lesion is as effective as treatment oral, but with fewer adverse effects
- LASER-argon, NdYAG and carbon dioxide—no results.
- surgical treatment—different types of surgical procedures, but not they are effective.

Cavernous hemangioma—are much less common as hemangiomas capillaries in children. They are mostly orbiting, single and well encapsulated, more common in women, manifests itself in late adolescence, do not have food prominent arterial, like capillary hemangiomas. They tend to spontaneous regression. It is possible to calcify.

Nevus Flammeu s—is a flat skin lesion of the eyelid, which does not disappear pressure. It has a bluish-purple hue, hence the name of the coming spots. It can occur separately or in association with Sturge-Weber syndrome. It requires no treatment, only of a cosmetic nature. Can be associated on the homolateral eye with glaucoma, diffuse choroidal hemangioma (possible erbium laser treatment).

Neurofibroma—in von Recklinghausen's disease plexiform tumor can affect the eyelid and orbit.

Precancerous Tumors

Actinic (solar) keratosis—with flat, shiny hyperkeratosis lesions, predisposing to spinocellular carcinoma.

Dubrenilh melanosis—pigmented macula with slow progression to melanoma requiring research of nodular thickening of the eyelid that suspects malignant transformation

Malignant Tumors

Basal Cell Carcinoma

- Is the most common eyelid tumour (90%) present in people in age, with localization lower eyelid 50%, internal angle 25%, eyelid upper 10–15% external Cantus 5–10%.
- Clinical
  - nodular tumor with shiny surface, pearlescent appearance with vessels dilated in the surface
  - nodular, ulcerated tumor with raised and rolled edges
  - sclerosing tumor with the appearance of endured plaque with well-defined edges
- Treatment
  - surgical with wide excision of the tumor by 3 mm in the area of normal skin
  - radiotherapy and cryotherapy for inoperable forms

Spinocellular Carcinoma

- Malignant tumor of the eyelid with 5% incidence localized in people in age, most commonly at the mucocutaneous junction, equally affecting those two eyelids: upper, lower, with possible preauricular metastases below mandible with indication surgical treatment.
- Clinically-hyperkeratosis erythematous plaque, hyperkeratosis nodular tumor or ulcerative tumor with endured, eversate edges.

Sebaceous Gland Carcinoma

- Rare tumor started from the meibomian glands in the form of a tumor nodular, with evolutions towards infiltrated carcinoma manifested by thickening eyelid margin and localized madarosis or carcinoma of the Zeiss gland with ulcerative or nodular lesions with slow growth at the edge of the eyelid.
- The tumor requires differential diagnosis depending on the clinical appearance with:
  - Relapsing Salazion—in nodular tumours
  - Chronic blepharitis, infiltrative blepharitis
  - Limbic keratoconjunctivitis—in pagetoid extension

Surgical treatment—excision and reconstruction of the eyelid. Recurrence is possible.

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Chapter 5
Ophthalmological Pathology of the Eye: Conjunctiva

Marieta Dumitrache

Abstract **Conjunctivitis** is an inflammatory infectious process, bacterial, viral, fungal, parasitic, chlamydial, allergic, autoimmune fibrosing granulomatous conjunctivitis (pemphigoid, epidermolysis bullosa) or non-autoimmune. **Bacterial conjunctivitis** forms are: hyperacute—gonococcal conjunctivitis of the new-born, acute—pseudomembranous, purulent, catarrhal conjunctivitis and chronic—catarrhal with acanthamoeba in contact lens wearers. **Conjunctivitis with chlamydia** caused by chlamydia trachomatis, serotypes D-K, is present in new-borns; it can be complicated with pannus, corneal leukoma. In adults, trachoma is a primary chronic keratoconjunctivitis with gradual evolution, followed by serious palpebral complications: trichiasis, entropion, corneal ulcer sequelae, pannus, corneal opacities, blindness, symblepharon. Trachoma requires continuous surveillance in the endemic area with appropriate preventive and curative treatment. Viral **conjunctivitis** forms are relatively common, have varied etiology, multiple clinical manifestations and can be associated with viral respiratory infections. **Allergic conjunctivitis** often has a chronic evolution, of variable intensity and is rarely associated with vision loss. They can be simple allergic conjunctivitis, vernal keratoconjunctivitis, phlyctenular. Rarely, but sometimes very seriously, there may be **parasitic, mycotic conjunctivitis. Granulomatous conjunctivitis**—TB, syphilis, sarcoidosis, may be present. **Fibrosing conjunctivitis in autoimmune** bullous diseases—pemphigus, and **non-autoimmune** in: trachoma, diphtheria, streptococcus. **Conjunctival degenerations** are pinguecula, pterygium. **Conjunctival tumors** are non-pigmented, pigmented, benign—nevus, **precancerous**—Bowen's tumor, **malignant** tumors, melanoma, carcinoma, lymphoma, Kaposi's sarcoma.

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The Conjunctiva is a richly vascularized translucent mucous membrane, which covers the posterior face of the eyelids, the palpebral conjunctiva and the anterior face of the eyeball bulbar conjunctiva that is inserted on the edge of the eyelid and into the around the cornea to the limb; the transition between the two portions of the conjunctiva is made at the level of the upper and lower conjunctival sac bottoms.

Conjunctivitis

- Conjunctivitis is an inflammatory process localized in the conjunctiva sectoral or diffuse, uni-or bilateral and represents one of the most common eye diseases
- Etiological classification of conjunctivitis:

Bacterial Conjunctivitis

- Hyperacute conjunctivitis
  - Gonococcal conjunctivitis of the newborn
- Acute infectious conjunctivitis
  - Catarrhal
  - Mucopurulent
  - Pseudomembranous
  - Membranous
- Chronic conjunctivitis
- Angular conjunctivitis

Chlamydial Conjunctivitis [1]

- Conjunctivitis with neonatal inclusions
- Conjunctivitis with inclusions of the adult [2]

- Pool conjunctivitis
- Trachoma

Viral Conjunctivitis [3]

- Adenovirus keratoconjunctivitis
  - Acute follicular conjunctivitis (B)
  - Epidemic keratoconjunctivitis
  - Pharyngoconjunctival fever
  - Hemorrhagic conjunctivitis
- Herpetic conjunctivitis
- Other viral conjunctivitis—varicella zoster virus, picornavirus, poxviruses, Epstein-Barr, measles, rubella

Allergic Conjunctivitis [4]

- Simple allergic conjunctivitis
- Vernal (spring)keratoconjunctivitis
- Atopic keratoconjunctivitis
- Flictenular keratoconjunctivitis
- Giganto-papillary conjunctivitis

MYCOTIC COJUNCTIVITIS
PARASITIC CONJUNCTIVITIS
GRANULOMATOUS CONJUNCTIVITIS

Fibrosing Conjunctivitis in Cutaneous Bullous Diseases-Autoimmune Mucous Membranes

- Autoimmune diseases of the basal membrane
  - Cicatricial pemphigoid
  - Bullous epidermolysis
- Intraepithelial autoimmune diseases
  - Pemphigus
  - Medicinal pemphigoid—Stevens-Johnson syndrome

Non-Autoimmune Fibrosating Conjunctivitis [5]

- Clinical signs depending on the etiology of the conjunctiva
  - Bacterial conjunctivitis

    acute onset, generally unilateral
    purulent discharge
  - Viral conjunctivitis

    acute onset, frequently bilateral
    watery secretion
    lacrimation, photophobia if the cornea is affected
    conjunctival follicles present
  - Allergic conjunctivitis

    acute, subacute, recurrent, bilateral onset or not associated with rhinitis allergic
    intense pruritus, lacrimation
    mucous discharge

Conjunctivitis in a newborn can be:

- toxic-by administering prophylactic silver nitrate in Credé prophylaxis
- gonococcal-occurs on Day 2–4 with adhering purulent discharge and risk of corneal damage
- with chlamydia-occurs on day 5–14 with mucopurulent secretion, edema palpebral, false membranes, keratitis
- herpetic-occurs on day 4–7 with blepharoconjunctivitis, and/or systemic corneal damage.

Conjunctivitis in a child is caused by: Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus, Moraxella.

Conjunctivitis in an adult is:

- bacterial-Staphylococcus aureus, epidermidis, Streptococcus pneumoniae, Escherichia coli, Neisseria gonorrhoeae, Pseudomonas, Proteus, Seratia. Unilateral, symmetrical, accompanied by purulent discharge with eyelid edema, chemosis and papillary hypertrophy; has rapid evolution 5–8 days.
- viral-adenovirus (most common), epidemic keratoconjunctivitis, HSV, hzv, Epstein-Barr, rubella, measles, unilateral with lacrimation, chemosis, painful adenopathy, +/- corneal injuries.

Bacterial conjunctivitis requires examination of conjunctival secretion with antibiogram to identify germs.

Sampling for laboratory examination of conjunctival secretion is required in:

- photophobia, chemosis, extensive eye oedema
- suspicion of bacterial superinfection, in pre-existing pathology conjunctival/corneoconjunctival of other cause (viral, allergic)
- decreased AV
- recent eye surgery
- patients
  - with corneal graft
  - immunodepressed
  - with underlying local pathology (corneal dystrophy, static disorders palpebral, lacrimal obstruction)
  - in ICU services (nosocomial infections)
  - special situations: monophthalm, children, wearers of eye prostheses
  - atypical conjunctival inflammation, recurrent conjunctivitis or in which the symptomatology does not improve after 7–10 days of treatment.**Clinical signs localized in the conjunctiva** [6]
- **Conjunctival hyperemia**-represents congestion of conjunctival vessels and it is present in inflammatory pathology of the conjunctiva, iridocyclitis and in acute glaucoma
  - conjunctival hyperemia may be:
  - acute, transient, through direct irritants: dryness, ambient, burns
  - chronic, recurrent in Alcoholics, foreign body, trichiasis, chemical burns
- **Conjunctival chemosis**
  - Is edema of the conjunctiva commonly associated with increased elasticity of tissues
  - Etiologic:

    local inflammations: conjunctivitis, comnean ulcer, endophthalmitis, meibomitis, orbital cellulitis, dacrioadenitis, dacryocystitis
    local obstructions with blood, lymphatic blockage in: tumors, exophthalmia endocrine, FCC, congestive glaucoma
    systemic causes: anemia, severe hypoproteinemia, heart disease, necrotic, angioedema
- **Bruising**—There are subconjunctival hemorrhages present in: trauma, inflammation conjunctival, spontaneous capillary ruptures (in diabetes, HTA), abnormalities vascular diseases (telangiectasias, aneurysms, angiomatous tumors), blood diseases (purpura, hemophilia).

- **Conjunctival Xerosis** (dryness) may be:
  - paremchymatous in: scarring in trachoma, diphtheria, Stevens Johnson, pemphigus, burns, proptosis, paralysis VII ectropion, lagophthalmia
  - epithelial in: hypovitaminosis A
  - causal and symptomatic treatment with: artificial tears (methylcellulose 0.7%, 0.3%, polyvinyl alcohol)
- **Symptoms in conjunctivitis**
  - Pruritus
  - stinging, burning sensation
  - foreign body sensation
  - eye discomfort
  - photophobia, lacrimation, blepharospasm, AV decrease, are present only if the cornea is affected
  - variable symptoms, depending on the patient and the type of conjunctivitis.
- **Objective clinical signs in conjunctivitis** [5, 6]:
  - Color changes
  - Changes in secretion
  - Relief changes

Color Changes

- ***Conjunctival hyperemia (congestion, redness)*** is:
  - superficial-is located in the bottoms of bags, light red color, disappears after adrenaline 0.1%.
  - present in: conjunctivitis, foreign bodies, external irritants (dust, smoke, pollen, contact lenses)
  - **deep**—localized perilimbic, violet-red color, does not disappear at adrenaline 0.1%.
  - present in: iridocyclitis, keratitis, episcleritis, uveitis, acute glaucoma

Secretion Changes

- ***Conjunctival hypersecretion***—inflammatory exudate of protein type (serous, mucous) or/and cellular (purulent)
  - serous: allergic, viral conjunctivitis
  - mucous: spring conjunctivitis, atopic keratoconjunctivitis

  - mucopurulent: bacterial conjunctivitis, chlamydial conjunctivitis
  - purulent: conjunctivitis with Neisseria gonorheae.

Relief Changes

- ***Membranes***—adhesions to the underlying epithelium that bleed upon removal in conjunctivitis diphtheria, betahemolytic Streptococcus.
- ***Pseudomembranes—***fibrino-cellular exudates, which can be easily removed without bleeding. In conjunctivitis with adenoviruses, Stevens-Johnson syndrome, gonococcal conjunctivitis, with Streptococcus pyogenes.
- ***Papillae***
  - vascular reaction in prolonged conjunctivitis
  - small formations, centered by a vascular axis, surrounded by stroma erythematous and hyperplastic epithelium by chronic inflammation:
  - in spring conjunctivitis, Contact Lens Wearers.
- ***Follicles***
  - small tarsal or limbic protrusions, with a clear, avascular Center
  - in TB, streptococcal, staphylococcal, mycotic, parasitic conjunctivitis
- ***Granulomas***—chronic inflammatory nodules by peripheral fibrovascular proliferation: in "Cat Claw disease", TB, syphilis, leptospirosis, foreign body body reaction (wood, insect wings, Caterpillar hair, cactus, suture material).
- ***Conjunctival ulceration***
  - in Stevens-Johnson syndrome, chemical/thermal burns
  - trauma
- Conjunctivitis progresses to healing in 5–10 days at a rate of 60%.
- The favorable course of a conjunctivitis is present in the first 48–72 h if treatment is appropriate.
- Unfavorable course of a conjunctivitis is possible if:
  - there is an outbreak of infection in the body
  - immunosuppression (tarati, HIV, diabetes mellitus)
  - limited response to treatment
  - resistance to the antibiotic used
- In the unfavorable course discontinue treatment 1–2 days, the examination is done conjunctival secretion and resume treatment after antibiogram.
- Local antibiotic treatment is indicated to shorten the course of the disease and prevent complications.
- **Isolated conjunctivitis does not result in decreased AV.**

- Purulent conjunctivitis requires bacteriological sampling for adequate antibiotic therapy.
- Non-purulent conjunctivitis can be of viral origin and requires only symptomatic treatment, if needed systemic antiviral treatment
- **Treatment with corticoid collars in supposedly herpetic conjunctivitis it is contraindicated.**
- Chronic and relapsing conjunctivitis may suspect impermeability of lacrimal paths to be checked.
- Conjunctivitis with lacrimation from birth requires the survey of lacrimal pathways.

Types of antibiotics used in the local treatment of conjunctivitis

- aminoglycosides: tobramycin (Tobrex), netilmycin (Nettacin), gentamicin (Genticol) 4 6/day
- fluoroquinolones: ciprofloxacin (Ciplox, Ciloxan), Ofloxacin (Floxal), lomefloxacin (Okacin) 4–6/day
- neomycin + polymyxin B + gramicidin (Colbiocin) 6/day
- fusidic acid: (Fucitalmic gel) 2/day
- chloramphenicol: (Sificetin) 4/day

Bacterial Conjunctivitis [5–7]

Bacterial conjunctivitis is infection of the conjunctiva by direct contact or by secretions with the following pathogens common), Staphylococcus epidermidis (blepharoconjunctivitis), Staphylococcus pneumoniacus (conjunctivitis associated with subconjunctival hemorrhages), Streptococcus hemolytic with pseudomembrane, Hemophilus, influenze (Aegyptus Koch Weeks-epidemic conjunctivitis in subtropical countries), Morax Bacillus-Axenfeld (angular conjunctivitis), Pseudomonas (corneal invasion), Neisseria gonorrhea (purulent conjunctivitis) corynebacterium diphtheria (rare), membranous conjunctivitis.

Clinical forms of bacterial conjunctivitis are different depending on the bacterium involved, its pathogenicity, the severity of the infection, the reactivity of the host.

- Depending on the evolution of bacterial conjunctivitis are hyperacute, acute, chronic

Hyperacute Conjunctivitis

Gonococcal Conjunctivitis of the Newborn

- Currently rare condition caused by contamination of the newborn in the moment of expulsion from the mother infected with gonococcus
- Clinical
  - development 2–3 days—with hyperacute onset, abundant purulent discharge, chemosis, preauricular adenopathy
  - pyorrhea-2–3 days-important purulent discharge, greenish-yellow with agglutination of cilia
  - regression
- Complications—progressive marginal ulcer (in the ring) with perforation and endophthalmitis
- Treatment
- prophylactic
  - of the mother for gonococcal infection
  - of the child-prophylaxis of cred (1% silver nitrate, erythromycin, tetracycline in the first hour of life)
- curative-local
  - antibiotic: ciprofloxacin, ofloxacin, gentamicin, penicillin, erythromycin every two hours
  - washings with saline every 30–60 min
- healing: when three consecutive secretions are sterile

Acute Conjunctivitis [8, 9]

Acute Catarrhal Conjunctivitis

It is the most common form of acute bacterial conjunctivitis and is characterized by conjunctival hyperemia and mucopurulent secretions [3].

- Etiology
  - chronic exposure to smoke, dryness, chemical irritants
  - local causes of irritation: trichiasis, foreign bodies, seborrhea
  - refractive errors, forelimbs, convergence failure

  - alcohol abuse, insomnia, metabolic disorders
  - bacterial infections

    Staphylococcus aureus (common)
    Gram-negative: Proteus, Klebsiella, Esclerichia Coli, Moraxela Lacunata

  - other infections-mucopurulent conjunctivitis, dacryocystitis, rhinitis, catarrh respiratory, exogenous infections

- Symptoms
  - foreign body sensation (through vessel engorgement)
  - average photophobia
  - mucopurulent secretion with agglutination of cilia
  - cessation of vision
  - sometimes halos colored to light by prismatic effect of corneal mucus
- Signs
  - light red conjunctival hyperemia
  - conjunctival chemosis
  - hemorrhagic spots in pneumococcus
- Complications—marginal ulcer, superficial keratitis, blepharitis, dacryocystitis
- Local treatment [10]
  - antiseptic colir and eye wash with sterile solutions 2 times/day
  - dark color lenses to reduce photophobia
  - **no eye dressing**
  - antibiotic colir-tobramicim rifampicin, norfloxacin in severe forms
- Systemic-NSAIDs-ibuprofen, paracetamol 2–3/day
- Differential diagnosis in conjunctivitis—Table 5.1

Table 5.1 Clinical differential diagnosis between different types of conjunctivitis

Clinical signs	Bacterial conjuncitivits	Viral conjunctivitis	Allergic conjunctivitis	Conjunctivitis with Chlamydia
Congestion	+++	+	+	+
Chemosis	++	+−	−	−
Sub-Conjunctival Hemmorhages	+−	+−	−	−
Secretion	Purulent	Watery	Watery	Mucopurulent
Papilla	+−	−	++	+−
Follicles	−	+	−	++
Pseudomembranes	+−	+−	−	−
Panus	−	−	Verenal Exception	−
Preauricular Adenopathy	+−	++	−	+−

Acute Purulent Conjunctivitis

- Affects adult, male and is produced by gonococcus, rarely Staphylococcus, pneumococcus.
- Clinical
  - acute conjunctivitis with abundant purulent discharge
  - may complicate: keratitis, iridocyclitis
- Treatment
  - eye washes to remove secretions
  - topical antibiotic: Tobramycin, bacitracin
  - atropine
  - systemic antibiotic therapy as needed

Acute membranous conjunctivitis

- It is characterized by the formation of membranes on the conjunctiva.
- Etiologically this type of conjunctivitis is produced by diphtheria, rare today, but occasionally conjunctivitis can be determined by hemolytic Streptococcus.
- Complicates with corneal ulcer and scarring-related complications with simblefaron, trichiasis, entropion, conjunctival xerosis.
- Treatment
  - topical-penicillin at 30 min
  - systemic

    antidiphtheria serum
    penicillin I. m. UK 2/day—10 days—prevention of simblefaron

Pseudomembranous Conjunctivitis

- Acute conjunctivitis characterized by the formation of pseudomembranes (exudate fibrinous coagulated) that detaches easily leaving the conjunctival epithelium intact
- Etiologically may be bacterial infection corinebacterium diphtheria with virulence low, Streptococcus Hemophilus influenzae, gonococcus Neisseria
  - viral infection-HSV, adenovirus
  - chemical irritants-ammonia, silver nitrate
- Clinical
  - acute mucopurulent conjunctivitis
  - white/yellowish pseudomembranes in the saccule and on the palpebral conjunctiva
- Topical and systemic (if necessary) etiological treatment.

Angular Conjunctivitis

- Is a chronic conjunctivitis localized in the internal angle (sometimes with interest of the skin).
- Etiology
  - Morax—Axenfeld Bacillus, rarely Staphylococcus
  - the source of infection is frequently the nasal cavity
- Complications
  - blepharitis
  - marginal corneal ulceration
- Treatment
  - prophylactic
  - personal hygiene
  - treatment of nasal infection
  - local-oxytetracycline 1% ointment 2/day 10 days.

Chronic Catarrhal Conjunctivitis [6, 7]

- Etiology
  - chronic exposure to smoke, dryness, chemical irritants
  - local causes of irritation: trichiasis, foreign bodies, seborrhea
  - refractive errors, forelimbs, convergence failure
  - alcohol abuse, insomnia, metabolic disorders
  - bacterial infections

    Staphylococcus aureus (common)
    gram-negative: Proteus, Klebsiella, Escherichia Coli, moraxela lacunata
  - Other infections-mucopurulent conjunctivitis, dacryocystitis, rhinitis, catarrh respiratory, exogenous infections
- Symptoms
  - chronic redness
  - burning sensation, foreign body, in the morning, with difficulty holding the eyes open
  - mucoid secretions in the cantus)
  - lacrimation

- Signs
  - congestion of conjunctival vessels and palpebral margin
  - papillary hypertrophy on the palpebral conjunctiva
- Treatment
  - Exclusion of favoring factors
  - Local

    antibiotic-chloramphenicol, gentamicin 3–4/day—14 days to elimination of inflammation
    astringent drops
- Contamination is made by:
  - prolonged course of an acute conjunctivitis or germ infection low virulence bacteria
  - the presence of a chronic neighborhood infection: dacryocystitis, chronic rhinitis
  - respiratory infections
  - exogenous infection

    by direct contact
    vector transmission
  - endogenous infection: meningococcus, gonococcus

Conjunctivitis in Contact Lens Wearers Requires

- Renouncing the port of contact lenses (or discarding them) until total healing
- if the inflammation is moderate, contact lenses may be used transiently with the administration of collars with Netacin.
- Common conjunctivitis may occur in contact lens wearers, or Acanthamoeba infection
- If the response to empirical treatment does not give a result, it is necessary to culture with antibiogram.

CHLAMYDIAL CONJUNCTIVITIS—Chlamydia are a group of intracellular microorganisms located between bacteria and viruses, with their own DNA and RNA [9].

Conjunctivitis with Neonatal Inclusions

- Is determined by Chlamydia trachomatis serotype D K, transmitted to child from mother at the time of expulsion
- Subacute onset in the first 5–12 days after birth, later than gonococcal conjunctivitis
- Signs
  - mucopurulent secretion associated with papillary and follicular reaction
  - eyelid edema +/− pseudoptosis
- Complications
  - peripheral corneal panus
  - corneal leukoma
  - conjunctival scars
- Differential diagnosis
  - bacterial conjunctivitis
  - gonococcal conjunctivitis with abundant purulent secretions
  - primo-herpetic infection (HSV2) with mucous secretions at 3–15 days.
- Treatment
  - local-tetracycline ointment 4/day
  - general-erythromycin ethylsuccinate 25 mg/kg 2/Day, 4 weeks
  - treatment of parents

Conjunctivitis with Inclusions of the Adult [5, 11]

- Is produced by Chlamydia trachomatis serotype D K transmitted from sexual infection
- uni or bilateral is a chronic conjunctivitis with mucopurulent secretion at a young adult
- Signs
  - important conjunctival hyperemia With Eyelid edema
  - papillary and follicular hypertrophy (in the lower sac fundus)
  - mucopurulent secretion
  - painless adenopathy
- Complications
  - peripheral corneal infiltrates
  - upper panus in chronic cases

- Treatment
  - local chloramphenicol 1% 4/day, tetracycline-pomade 4/Day 6 weeks
  - systemic

    azithromycin—1 g
    doxycycline-300 mg/Week 3 weeks, 100 mg/day l–2 weeks
    tetracycline-250 mg 4/Day, 6 weeks
    erythromycin-250 mg 4/Day, 6 weeks if contraindicated tetracycline.

Pool conjunctivitis—The etiopathogenic agent is clamidosome oculo-genitalis, serotype d-K.

- Present in children and young people attending swimming pools
- Uni -, bilateral rapid
- Signs
  - lacrimation, photophobia
  - eyelid edema, conjunctival
  - Medium mucopurulent secretion
  - opalescent follicles on the tarsal conjunctiva and in the sacs
- Complications-corneal damage
- Treatment-similar to conjunctivitis with inclusions of the adult

Trachoma [1, 9, 11, 12]

- Is a primary chronic keratoconjunctivitis affecting simultaneously superficial epithelium of the conjunctiva and cornea. Conjunctiva reacts by the development of follicles and papillae.
- Serotypes a, B, B2, C of Chlamydia trachomatis are associated with hyperendemic trachoma, and serotypes D K with paratrachoma (chlamydia oculogenitalis).
- Predisposing factors: age [child, gender (women), climate (dry), socio-status-economically (in disorganized groups, poor, without water,without education).
- Endemic areas, Africa, India, Middle East, Southeast Asia
- **Trachoma is the leading cause of preventable blindness, 10–15% of causes of World blindness** [1].
- Incubation period 5–21 days.
- Insidious, subacute, rarely acute onset.
- In endemic areas, conjunctivitis occurs in the first decade of life (often neglected, with a clinical appearance of banal conjunctivitis), with slow progression; sequelae of the disease are established after 20 years of evolution, with incidence maximum blindness between 40 and 50 years.

- Stage evolution
- Possible reinfections, recurrences, other infections

Classification of Trachoma—FISTO-1987

TF-Follicular Trachomatous Inflammation
- Bilateral. Insidious with lacrimation
- Thickened Conjunctiva, > 5 follicles on the tarsal conjunctiva, superior, with fine perilimbic vascular areas
- Presence of Prowacek corpuscles in the scraper product of the conjunctival epithelium.

TI-Trachoma Florid (Fig. 5.1)
- Intense trachomatous inflammation with grayish yellow multiple follicles, gelatinous appearance (fish roe) that break under pressure, and expand to the cornea and Tarsus, panus.
- Palpebral pseudoptosis

TS-Trachoma Precicatriceal (Fig. 5.2)
- Numerically reduced follicles
- Scars on the tarsal conjunctiva
- Extended Panus
- Arlt line parallel to the free edge of the eyelid

TT-Cicatricial Trachoma with Trichiasis
- Follicles disappear, scars present
- Complications: simblefaron, entropion, trichiasis, vascularized leukoma

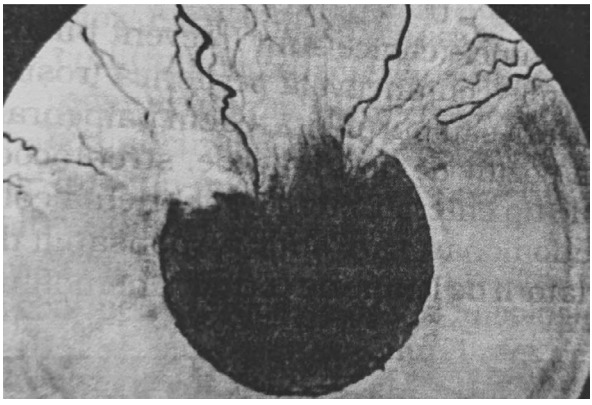

Fig. 5.1 Trahoma-Panus Trahomatos

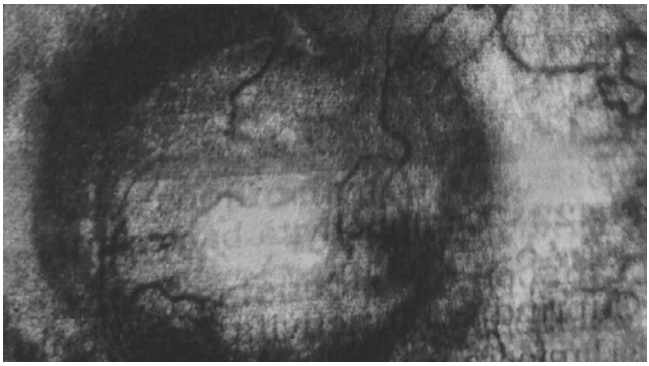

Fig. 5.2 Stage IV Trachoma

TO-Corneal Opacities

- Dense scars that cause decreased/loss of vision
- Serious complications
  - corneal ulcer with possible bacterial infections
- Sequelae
  - eyelids: trichiasis, entropion, tilosis (thinning of the edge of the eyelid), ptosis, madarosis, ankyloblefaron
  - conjunctiva: xerosis, simblefaron
  - cornea: xerosis, Panus-blindness, opacities, corneas
  - other sequelae: chronic dacryocystitis, dacrioadenitis
- Treatment [2, 6]
  - **Prophylactic**

    local, personal hygiene
    isolation and treatment of contacts
    topic

    tetracycline 1% ointment 5 days/Month, 6 months
    chloramphenicol ointment
    erythromycin 0.5% 2/day, 6 weeks, break 6 weeks
    general-azithromycin 1 g/p.o. in endemic areas [2]
  - **curative**

    local: cholirs, ointments with antibiotic, tetracycline, erythromycin 4/Day 6 weeks
    general

    tetracycline, erythromycin 250 mg orally 6/Day, 3 4 weeks or
    doxycycline 100 mg orally 2/day, 3-4 weeks
    azithromycin 1 g/day

- **Sequelae—trichiasis**

  epilation, electrolysis, cryolysis
  entropion-surgical
  xerosis-artificial tears

VIRAL CONJUNCTIVITIS—Are relatively common diseases (15%), have varied etiology and manifestations multiple clinical manifestations and may be associated with respiratory viral infections [12–14].

Adenovirus Keratoconjunctivitis
- Is the most common cause of viral conjunctivitis
- Specific signs
  - conjunctival follicles
  - serous secretion
  - regional preauricular, submandibular lymphadenopathy

***Acute Follicular Conjunctivitis-Beal*—Endemic Serotypes 1, 2, 3, 4**
- Mild sympathomatology
- Presence of small tarsal follicles, semilunar envelope, caruncle
- There may also be subacute forms
- Treatment-symptomatic nonspecific: artificial tears (Eyestil, Lacrisifi).

***Epidemic keratoconjunctivitis*—Serotypes 5, 19, 37**
- Sudden, severe onset with hyperemia, serous secretion, preauricular nodule-spainful, subconjunctival haemorrhage, follicles
- Complications
  - it is associated in children with severe infections: otitis, diarrhea, pharyngitis
  - evolution of keratitis 7–14 days
  - corneal complications in 80% of variable cases: punctate keratitis superficial, unilateral, diffuse keratitis, stromal infiltrates, uveal reaction
  - children are more susceptible to viral conjunctival infection, and adults to bacterial conjunctival infection
- Treatment
  - symptomatic, nonspecific, artificial tears
  - antibiotic: Tobradex, Maxitrol, Spersadex
  - for corneal lesions, topical corticoids-Maxidex, Flumetol

***Pharyngoconjunctival Fever*—Serotypes 3, 7, 2, 4, 7, 14**
- moderate symptoms of catarrhal, follicular conjunctivitis with reduced secretion, serosis
- pharyngitis
- many viral conjunctivitis are self-limited, after an evolution of 10–14 days without antiviral treatment

***Hemorrhagic Conjunctivitis*—Enterovirus 70, coking virus a 24**
- conjunctival haemorrhage
- self-limited

Treatment
- symptomatic nonspecific: antiseptic to limit the risk of bacterial superinfection, artificial tears
- topical antiviral: idoxiuridin, trifluridin, vidarabin, Acyclovir ointment 3%, cidofovir in the treatment of keratoconjunctivitis
- **Caution in topical corticoid treatment in HSV**

Herpetic Conjunctivitis—Most Commonly, Produced by HSV1 [15]**.**
- may occur as a primary or recurrent infection with or without palpebral or corneal blisters
- clinically typical or atypical follicular conjunctivitis
- punctate, dendridic, stromal (disciform)epithelial corneal lesions, uveitis

Complications—possible corneal damage, dry eye syndrome.
Treatment-primary infection is self-limited

- local
  - antiviral-Acyclovir, Ganciclovir ointment 5/day until healing
  - corticoids contraindicated in epithelial keratitis
- systemic
  - acyclovir 600–800 mg 5/day, 10–14 days or
  - famciclovir 5/day, 7 days

Other Viral Conjunctivitis

HZV (zoster) requires local and general Acyclovir.
Picornavirus—hemorrhagic conjunctivitis.

Poxviruses
- *molluscum contagiosum*
- unilateral progressive onset with moderate secretion
- treatment-excision, cryoapplications, cauterization

Epstein-Barr Virus in Mononucleosis
- follicular conjunctivitis associated with pharyngitis, febrile syndrome
- complications: epithelial, stromal keratitis, multifocal choroiditis with panuveitis***Measles, rubella virus***

Allergic Conjunctivitis [16]

- Are inflammation of the conjunctiva by immediate hypersensitivity (humoral) or late (Cellular) to various allergens.
- Allergic conjunctivitis are the most common eye allergy, have frequent chronic course, with symptoms of varying intensity, very rarely associated with decreased vision
- have periodic, seasonal evolution, caused by various allergens: pollen, spores, dust

Simple allergic conjunctivitis—allergies to various allergens: pollen, Caterpillar hair, seasonal or perennial allergies.

Clinical:

- conjunctival hyperemia with pruritus and moderate papillary hyperplasia
- clear or sometimes affected cornea with limbic infiltrate, neovascularization in Atopic KC, panus, corneal ulceration in Vernal KC

Treatment—elimination of allergens (if possible).

Treatment in Allergic Conjunctivitis should be carried out quickly depending on clinical aspect [4]

- allergen identification and desensitization
- discontinuation of contact with allergens
- eye decongestants
  - adrenergic agonists-tetryzolin, phenylephrine, oxymetazoline, naphazoline (Nafagal, Naphcon, Proculin) (Ocuclear, Visine)
  - antihistamines topically: Emadin, Oftazolin, Spersalerg, Ischemol, Zaditen
- Systemic
  - oral antihistamines generation I, II-chlorpheniramine, diphenhydramine, Promethazine, Loratadine, Ceftrizine
  - side effects: dry eyes, mouth, hypotension, peptic ulcer, closed-angle glaucoma
- Topic
  - NSAIDs-Acular, Voltaren, Nevanac, Prolensa
  - topical steroids in severe allergic diseases or with chronic course in: kerato-conjunctivitis Vernal, atopic-Alrex, Lotemex, FHL, Predfort
  - immunomodulators in severe forms: ciclosporin 0.05% (Restazis), tacrolimus 0.1%, 0.3%, ointment (Protopic)

Clinical forms of allergic conjunctivitis:

- Acute conjunctivitis: seasonal and perennial allergic conjunctivitis
- Chronic conjunctivitis: Vernal, atopic, gigantocellular, flictenular keratocon-junctivitis

Vernal (Spring) Keratoconjunctivitis (Fig. 5.3)

- Patient with extraocular allergic manifestations, family history of atrophy, 4–20 years old, boy, summer (in the tropics)
- It is a reaction to an exogenous allergen (pollen) on an atopic plot
- Bilateral, child with pruritus, lacrimation, photophobia, frequent blinking
- Three clinical forms:
  - palpebral-diffuse palpebral papillary hypertrophy on the upper Tarsus which takes the look of, paving stone", associated with Limbic burelet
  - bulbar, with conjunctival congestion and gelatinous accumulations around limbo
  - the mixed form combines the two forms
- there may be corneal lesions: epithelial punctate keratitis, ulcerative keratitis, pseudogerontoxon
- the disease can self-limit spontaneously after ten years, but presents many long-term recurrences

Local treatment

- vasoconstrictors
- antihistamines
- Darkened glasses
- mast cell membrane stabilizers-sodium Cromoglicate 2–4% 3/day
- acetylcysteine
- non-steroidal anti-inflammatory drugs
- corticoids in severe forms

Fig. 5.3 Allergic (Vernal) conjunctivitis

Atopic Keratoconjunctivitis

- Young patients with atopic dermatitis—eczema.
- Onset in childhood with chronic irritation and photophobia.
- Signs
  - chronic inflammation at the edge of the eyelid (staphylococcal, angular blepharitis)
  - milky appearance of the tarsal conjunctiva with hyperemia and fine papillae
  - superficial punctate keratitis with neovascularization
  - may be associated with keratoconus

Treatment
- local
- artificial tears (without preservative)
- corticoids locally, as needed, tarsal injection
- mast cell degranulation inhibitors
- cyclosporine in rebellious forms
- systemic
  - antihistamines
  - Azithromycin 500 mg/day 3 days
  - Cyclosporine

Flictenular Keratoconjunctivitis

Associated with TB, subacute chronic infections.
Present in 3–15 years, more common in girls in the warm season.
There are three clinical forms:

- simple flictenular conjunctivitis with conjunctival nodules near the limb, pinkish on the bulbar conjunctiva, surrounded by a hyperemic area; time, these nodules can ulcerate
- necrotizing conjunctivitis with flictenes, with necrosis and ulceration
- miliary flictenular conjunctivitis-multiple flictenes

Treatment
- local
- steroids-dexa-or beta-metazone
- antibiotic-colir, ointment
- atropine
- specific—treatment of tuberculosis, septic focus (adenoid, caries) parasitic infection

Gigantopapillary Conjunctivitis

Chronic inflammatory process produced by a persistent mechanical irritation with hypertrophy of the papillae at the level of the superior tarsal conjunctiva, favored use of contact lenses, suture threads.

Treatment
- removing contact lenses
- artificial tears
- antiallergic

Mycotic Conjunctivitis

Fungal Infection with Rhinosporidium

- in children in endemic areas, humid tropical climate
  - clinical-flat, sessile, limbic or bulbar tarsal granulomas that bleeds easily in microtraumas
  - surgical treatment

PARASITIC CONJUNCTIVITIS—The most common are: cysticercosis, echinococcosis, filariasis, miaza [3].

Filariasis—It is determined by onchocerca volvulus and loa-loa.

- Filaria can get under the conjunctiva.
- Treatment
  - mechanical removal
  - diethylcarbamazine.

GRANULOMATOUS CONJUNCTIVITIS—Are granulomatous conjunctival inflammation in TB, syphilis, sarcoidosis, leprosy, tularemia.

Parinaud's Oculoglandular Syndrome

It is characterized by:

- unilateral granulomatous (nodular) conjunctivitis
- preauricular adenopathy

- fever
  - Present in tularemia, cat's claw disease, TB, syphilis, lymphogranulomatosis
  - Treatment:

    Local—broths or ointments with antibiotics: ciprofloxacin, gentamicin
    General—rifampicin, ciprofloxacin, trimethoprim-sulfamethoxazole, gentamicin 5–7 mg/kg/day, IV.

Fibrous Conjunctivitis in Autoimmune Cutaneomucous [5, 6]

Autoimmune Diseases of the Basal Membrane

- ***Cicatricial pemphigoid***

Autoimmune disease with Type II hypersensitivity and antibodies basal antimembrane.

Bilateral and mucocutaneous eye lesions with onset in older people

- Clinical
  - subepidermal, subepithelial bubbles and scars on the oral mucosa (85%), conjunctiva (65%), skin (25%) with bubble rupture in 2–3 days with erosions and ulcerations that heal with scar;
  - subepithelial conjunctival fibrosis in the tarsal conjunctiva upper and lower extensive, progressive, towards the butts with simblefaron, ankiloblefaron;
  - appearance of dry eye syndrome;
  - neovascularization and corneal keratinization, bacterial superinfection, corneal perforation
  - Complications: dry eye, trichiasis, recurrent corneal ulcer scarring corneal with blindness, conjunctival keratinization.
  - Treatment
- Local
  - corticoids in the acute phase
  - artificial tears
  - antibiotics for bacterial superinfection
  - subconjunctival injections of mitomycin (limit the progression of conjunctival scarring).
  - therapeutic contact lenses for corneal protection;

    systemic-corticoids in acute spurt

  - Dapson (Disulon) 100 mg/day in moderate forms (produces hemolytic anemia and methemoglobinemia)
  - immunosuppressants: methotrexate, cyclophosphamide

  - Surgical
  - of complications: cicatricial entropion, dry eye: tarsoraphia, keratoprosthesis, oral mucosa graft

- ***Bullous epidermolysis***

Intraepithelial Autoimmune Diseases

- ***Pemphigus***—the accompanying forms of conjunctivitis are:
  - Vulgar pemphigus (does not evolve to fibrosis)
  - Paraneoplastic pemphigus (associated with non-Hodgkin's lymphoma and bronchial cancer)
- Clinical
  - painful oral erosions
  - papillary conjunctivitis, ulceration, fibrosis
- Treatment
  - vulgar pemphigus-corticoids 1–2 mg/kg/day—immunosuppressants
  - paraneoplastic pemphigus—for conjunctivitis, local cortisone
- ***Medicinal pemphigoid***

Fibrosing conjunctivitis caused by long-term choleritis: antiglaucomatous (timolol, pilocarpine), antiherpetic (idoxiuridin).

Stevens-Johnson Syndrome—Cutaneous-mucosal syndrome by Type III hypersensitivity reaction triggered infection or medication [16, 17].

Causes of Stevens-Johnson syndrome

- bacterial infections: mycoplasma pneumonia, TB, Streptococcus, cat claws disease
- viral infections: HSV, mumps, influenza, mononucleosis, adenovirus
- drugs: antibiotics-penicillin, sulfamide, anticonvulsants—phenytoin, NSAIDs, barbiturates
- immunodepressed, AIDS

Clinical

- acute onset with fever, headache, general condition, rash symmetrical mucous membranes on the face, hands, feet, chest
- red, photophobic eyes with papillary conjunctivitis, blepharitis, episcleritis, corneal erosions
- late—progressive conjunctival fibrosis with simblefaron, scarring palpebral with entropion, trichiasis, dry eye

Systemic—skin lesions, mucous membranes (oral).
Treatment

- local
  - lubricants
  - corticoids
  - broad-spectrum antibiotic
  - conjunctival debridements
- other measures
  - occlusion of lacrimal points
  - frequent debridements
  - therapeutic contact lenses
  - surgical treatment entropion, trichiasis, oral mucosa graft for restoring bag butts
  - limbic stem cell transplantation
  - perforating keratoplasty
- keratoprosthesis.

Non-Autoimmune Fibrosing Conjonctivites

- Bacterial conjunctivitis: trachoma, diphtheria Bacillus, Streptococcus;
- Viral conjunctivitis: keratoconjunctivitis with adenoviruses;
- Systemic diseases: sarcoidosis, scleroderma, SJS Syndrome;
- Allergy, atopy; blepharoconjunctivitis, atopic keratoconjunctivitis, Stevens-Johnson syndrome, Lyell syndrome;
- Other causes: irradiation, ichthyosis, rosacea.

Woody Conjunctivitis

- Progressive onset in children with flictenular conjunctivitis associated with false membranes and Woody induration of the tarsal conjunctiva
- Similar lesions oral mucosa, pharynx, respiratory tract
- Treatment
  - corticoids
  - cyclosporine

Conjunctival Degeneration [12]

Pinguecula

- Common in the elderly adult with risk factors: sun exposure, irritation chronic conjunctival, dry eye
- Clinical-unilateral, bilateral, yellowish-white protrusion perilimbic, nasal or temporal, asymptomatic, variable size, which can become inflamed.
- Treatment
  - not necessary if growth is slow or absent
  - collir with corticoids (Flumetol, Maxitrol)
  - surgical excision if it is large in size, has recurring, aesthetic inflammation.

Pterygium

- Degeneration of the bulbar conjunctiva after exposure to irritating factors (dust, wind, dust), UV radiation, microtraumas.
- Signs
  - triangular fibrovascular proliferation from conjunctiva to cornea (adherent head and movable body)
  - Stocker line before the head
- asymptomatic in the early stages
- in extensive growth may occur AV decrease, restriction of movements ocular, dry eye
- Treatment
  - In early forms-local corticoids
  - In advanced forms

    surgical excision associated with conjunctival autograft, or amniotic membrane
    lamellar or perforating keratoplasty
    mitomycin, irradiation to reduce recurrences
  - In relapsed pterygion-McReynold operation with transplantation of pterygioma in the bottom of the lower sac; followed by beta irradiation. In recalcitrant forms surgical excision is associated with lamellar keratectomy and lamellar keratoplasty.

Pseudopterygium—Secondary inflammatory process in which a fold of the bulbar conjunctiva it remains attached to the cornea.

Xerosis of the Conjunctiva

- Epidermoid metaplasia of the conjunctiva
- Clinical forms
  - epithelial xerosis by Vitamin A deficiency is localized on bulbar conjunctiva (Bitot plate)
  - parenchymal xerosis, secondary to an eye condition: burning, trachoma, pemphigus
- Treatment-transplantation of the Stenon canal into the fundus of the conjunctival sac

Sessile Papilloma

- isolated lesion of the juxtalimbic bulbar conjunctiva
- treatment-excision

Conjunctival Cyst

- ***Congenital cyst***
- ***Retinal cyst***—may be present in chronic inflammation in pemphigus trachoma, localized more frequently in the superior fundus sac
- ***Post-traumatic epithelial cyst***
- ***Parasitic cyst***

Possible indication of surgical excision if needed with histopathological examination after clinical examination.

Conjunctival Tumors [3, 5]

- ***NON-PIGMENTED TUMORS***
  - Congenital-dermoid cyst and lipodermoid
  - Benign-granuloma, papilloma, adenoma, fibroma, angioma

  - Premalignant-intraepithelial epithelioma (Bowen's tumor)
  - Malignant-epithelioma or squamous cell carcinoma, squamous cell, basal cell carcinoma
- ***PIGMENTED TUMORS***
  - Benign-conjunctival nevus
  - Melanotic precancerous—Pete Hutchinson
  - Malignant-primary-malignant melanoma

Benign Tumors

Dermoid Cyst

- smooth, yellowish subconjunctival mass in young individuals
- treatment-excision, lamellar graft of cornea or sclera for bulky injuries
- associations:
  - ocular-palpebral coloboma, ocular coloboma, aniridia, microphthalmia
  - systemic-Goldenhar syndrome, Treacher-Collins Franceschelli

Lipodermoid

- congenital white/yellowish subconjunctival formation located at external angle
- possible postexcision cicatricial complications: ptosis, corneal dryness, oculomotor disorders

Pyogenic Granuloma

- burjoned, vascularized conjunctival formation after surgical trauma
- treatment-Excision and cauterization

Precancerous Tumors

Bowen's Tumor
- intraepithelial epithelioma (carcinoma in situ)
- rare precancerous lesion with vascularised reddish grey limbic localization
- treatment-excision

Pigmented Benign Tumors

Conjunctival Nevus

- Onset in the first decades of life and are intraepithelial pigmented lesions, well delimited, flat or slightly raised, generally located juxtalimbic.
- Signs of malignancy
  - localization on the palpebral conjunctiva or in the formix
  - corneal extension
  - gross increase in volume and/or pigmentation
  - vasculature
- treatment-excision for aesthetic purposes, in case of irritation, in suspicion of malignant transformation

Malignant Tumors-Intraepithelial Melanosis

Melanoma

- it can be de novo malignant conjunctival tumor, located towards the limb or by degenrescence of a nevus (rarer) with higher frequency in people older than 60
- clinical juxtalimbic black node
- treatment
  - excision with cryocoagulation for circumscribed tumors
  - diffuse tumors if possible excision, cryotherapy, mitomycin C
  - when needed enucleation, exenteration depending on tumor extension

Carcinoma

- *Spinocellular carcinoma*—pink, gelatinous lesions frequently juxtalimbic associated with blood vessels neoformation.

Fusiform cell carcinoma—it resembles squamous carcinoma, but is much more aggressive.

Carcinoma sebaceous glands—protruding plaque located on the tarsal conjunctiva.

All types of carcinoma require:

- surgical excision and adjuvant cryotherapy
- mitomycin or 5-fluorouracil in recurrence

Lymphoma

- pink salmon formation localized in the bottom, upper sac and surface of the eye that evolves slowly, bilaterally
- treatment-radiotherapy, chemotherapy, excision, cryotherapy

Kapossi Sarcoma

- bright red formation, frequently located in the bottom of the lower sac in the patient with AIDS
- treatment-radiotherapy, excision with or without cryotherapy

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Chapter 6
Ophthalmological Pathology of the Eye: Sclera

Marieta Dumitrache and Elena Dorina Popa

Abstract The **pathology of the sclera is predominantly infectious—inflammatory** and includes **EPISCLERITIS** and **SCLERITIS**. **Episcleritis nodular 20%, simple, episcleritis 80%,** are relatively benign, usual self limited, conditions present more common in young women, 40 years, with recurring episclere damage. The etiology of episcleritis is often difficult to define: idiopathic, associated with systemic manifestations (rheumatoid arthritis, tbc, Lyme, syphilis). **Scleritis** are severe diffuse or localized chronic inflammation of the sclera associated with systemic immunological diseases or infections. Scleritis are: **anterior** 98% (non-necrotizing 85%), necrotizing 13%, with inflammation, without inflammation (scleroderma perforans) and **posterior scleritis** 21%. Local treatment corticoids is indicated in episcleritis, anterior scleritis and systemic corticoid (oral i.v.), immunosuppresive agents **indicated** in severe forms of scleritis.

Keywords Episcleritis · Scleritis anterior · Posterior necrotizing · Non-neurotizing

The Sclera is an opaque fibrous structure that forms together with the cornea external tunic of the eyeball.

- The sclera continues with the cornea at the sclero-corneal Limbe, is covered at outer by the posterior Tenon capsule, and anterior by the bulbar conjunctiva which is inserted into the sclero-corneal Limbus.
- On the internal face sclera is in contact with the choroid with a supracoroidal space between them.

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On its surface the sclera shows three open spaces:
- posterior-around the optic nerve, where no, vessels and nerves pass short and long ciliary
- medium-posterior to the equator there are 4 zones for vorticous veins
- anterior-3–4 mm from the limb where the ciliary vessels pass

The histology of the sclera comprises the following layers [1]:
- Episclera-thin vascularized layer, covering the sclera
- Sclera-avascular structure consisting of collagen strips crossed in all directions to increase its resistance
- Lamina fusca-in contact with the supracoroidal and supraciliary space.

Infectious Inflammatory Diseases of the Sclera [2]

The pathology of the sclera is predominantly infectious-inflammatory and includes EPISCLERITIS and SCLERITIS.

Episcleritis

Episclerites are relatively benign, usually self-limited, conditions present more common in young women, 40 years, with recurring episclera damage, 33%, 67%.

- **Most episclerites are etiologically idiopathic, some episclerites can be associated with systemic diseases—rheumatoid arthritis or vasculitis, with rosacea, psoriasis, gout, infections, TB, syphilis, Lyme disease [3].**
- Episcleritis is a negranulamatous inflammation of the episcleral tissue with vascular dilations and lymphocytic-plasmocytic infiltrate.

The etiology of episcleritis is often difficult to define
- idiopathic—most episcleritis
- associated with systemic manifestations
  - rheumatoid arthritis or systemic vasculitis
  - infections-TB, syphilis, Lyme disease
  - gout, rosacea, psoriasis
  - dry eye syndrome

Symptoms
- asymptomatic
- burning sensation and foreign body
- rarely photophobia, lacrimation
- low, medium intensity eye pain
- **visual acuity is normal**

Clinical signs
- Pink, "salmon" redness located in a sector of the episcleral
– Episcleral node small, firm, single, multiple (rare), orange pink, mobile, covered by hyperemic conjunctiva.
– superficial episcleral vessels with radial disposition, which are seen through conjunctiva
– episcleral nodule can sometimes be associated with corneal changes type
– Deelen and peripheral infiltrates and rarely 10% with anterior uveitis.

Clinical forms
- simple episcleritis-80%, which can be sectoral or diffuse and can resolve spontaneously in 1–2 weeks
– nodular episcleritis-20%—persisted for a period of time
– in case of relapses, prolonged episcleritis pusee, resistant forms treatment, the patient should be fully clinically investigated for the establishment of etiology

Simple Episcleritis

Simple episcleritis is the most common form of localized primary episcleritis in the anterior portion of the episclera, recurrent, sometimes with spontaneous resolution.

Clinical
- localized conjunctival and episcleral hyperemia, extensive on one, not more than two dials
– expansion of the episcleral vessels with vessels that have a radial disposition that can be seen through the conjunctiva
– rarely-eyelid edema and conjunctival chemosis.

The course of episcleritis is variable: spontaneous resolution without treatment in 7–10 days, persists under local steroid treatment or relapses after 1–2 months.

Episcleritis does not advance to deep scleral inflammation.
In severe, relapsed forms, systemic cortisone treatment is required.

Nodular Episcleritis

Ocular symptoms are more intense and accentuate over time with:
- eye discomfort
– lacrimation, photophobia
– medium or intense eye pain, amplified with eyelid movements
– red eye with the visibility of the episcleral nodule covered by the hyperemic conjunctiva.

Clinical
- small episcleral nodules, orange pink, in a sector of the episclera, mobile, prominent, covered by hyperemic conjunctiva, located 2–3 mm from the limb

– nodules located more frequently anteriorly, before the insertion of the right muscles, less often posterior

The course of episcleritis is on average 10 days to 3 weeks with resolution spontaneous and possible relapses.

The positive diagnosis of episcleritis is given by the clinical examination and the **test with phenylephrine 10%,** which allows differential diagnosis between conjunctivitis and episcleritis

– a drop of neosinephrine 10% is instilled into the bottom of the inferior conjunctival sac, after which conjunctival hyperemia disappears completely, in a few minutes in conjunctivitis, but conjunctival hyperemia persists in episcleritis

Differential diagnosis episcleritis / scleritis—Table 6.1.

Treatment [4]

- it is necessary to establish etiology
- treatment
  - local-NSAID-Naphazoline
  - systemic-NSAID-indocid 25 mg 2/day
- ibuprofen 800 mg/day
- Phenylbutazone in nonresponsive or recurrent forms:
  - corticotherapy-topical 3.5/day
  - oral 1–1.5 mg/kg/day

Sclerites [5]

Sclerites are severe diffuse or localized chronic inflammation of the sclera, associated with systemic immunological diseases or infections that can cause significant AV decreases.

– low incidence, can be uni/bilateral
– affects patients between 40 and 70 years, more frequently.

Table 6.1 Clinical differential diagnosis episcleritis/scleritis

Clinical	Episcleritis	Scleritis
Affected vascular plexus	– Superficial	– Profound
Pain	– Moderate	– Intense
Episcleral vessels	– Radial	– Numerous, cross-cutting, “networked” aspects
Color	– Salmon pink/ orange-violet	– Lilac
Neosinephrine test	– Positive	– Negative

Diagnosis and treatment of these conditions should be quick and tailored clinical case (possibly etiopathogenic) to prevent serious visual sequelae with major impairment of visual function.

Primary Scleritis

- It is a chronic, painful inflammatory disease, commonly associated with diseases systemic autoimmune diseases.
- Primary scleritis can be: anterior, posterior and very rarely concomitant.
- Scleritis is accompanied by a decrease in AV more often by complications: keratitis, uveitis, cataract, glaucoma, associated DR.

The etiology of sclerites can be [2]:

- Idiopathic
- Autoimmune collagen diseases and vasculitis—about 50% of sclerites.
- Inflammatory
  - rheumatoid arthritis
  - atrophying Polychondritis
  - Wegener's granulomatosis
  - Behcet's disease
  - inflammatory diseases of the intestis
  - LES
  - Reiter syndrome
  - Giant cell arteritis
  - sarcoidosis
- Metabolic diseases: gout, porphyria, thyrotoxicosis
- Infectious
  - bacterial (extension of a bacterial keratitis)
  - fungi (rare)
  - viruses-HSV, HZV
  - parasites
  - complications in the exeresis of the pterygium
- Granulomatous diseases: TB, syphilis, sarcoidosis, leprosy.
- Trauma: chemical burns, irradiation, foreign bodies, Pseudomonas, Staphylococcus aureus, epidermidis, streptococcus pneumonia.
- Postoperative in late eye surgery (after 6 months)
- Anatomical classification of sclerites
  - anterior sclerites 98%—scleral inflammation before the equator
  - posterior sclerite-2%—scleral inflammation behind the equator
- Clinical classification of primary sclerites (Table 6.2)
  - anterior scleritis—98%

Table 6.2 Clinical classification of scleritis [1, 4]

Anterior sclerites—98%	Non-necrotizing—85% – Diffuse – Nodular
	Necrotizing—13% – With inflammation – Without inflammation—Scleroderma perforans
Posterior sclerites—2%	

non-infectious—85%

diffuse
nodular-deep scleral node, red, orange, Immobile, separated from the episclera

necrotizing—13%

with inflammation-painful scleral necrosis, with severe inflammatory lesions
no inflammation

scleromalacia perforans-scleral necrosis without inflammatory signs
asymptomatic with uvea exposure in women with rheumatoid arthritis

– posterior scleritis—2% with:

proptosis
significant AV decrease
restrictive motility
complications: choroid folds, exudative DR, papillary edema, glaucoma closed angle, lower palpebral retraction when looking up

Infectious Scleritis

- exogenous
  - posttraumatic
  - post-surgical-surgical interventions in pterygium, strabismus
  - extension of a neighborhood infection
- endogenous
  - bacterial: syphilis, TB, leprosy
  - viral HZV
  - fungi (rare)
  - extension of a neighborhood infection

Paraclinical examinations to confirm etiology in sclerites:
- TB-I. d. r. tuberculin, RX pulmonary graph
- Syphilis-VDRL

- Viral infections-HSV, HZV-P. C. R.
- Rheumatoid arthritis-rheumatoid factor-F. R.
- Systemic vasculitis
  - Nodular polyarthritis-ANCA-p
  - Wegener-ANCA-c, RX chest graph
  - Churg Strauss-eosinophilia, ANCA-P
  - Horton-temporal artery biopsy, antinuclear factor
  - Cogan-audiogram, cardiovascular examination
  - Bechcet-circulating immune complexes
  - Dermatological diseases-SLE-antinuclear factor
  - Sarcoidosis, psoriasis, Crohn's, Lyme, gout-enzyme-converting angiotensin, phosphocalcium balance
  - Idiopathic-elimination diagnosis
- **Negative neosinephrine Test with persistence of hyperemia after a drop of neosinephrine**
- In posterior sclerites: AFG, ultrasound B, scanner, orbital MRI (sclera thickness)
- Conjunctivo-scleral biopsy in:
  - necrotizing scleritis in the absence of an Associated autoimmune disease, to eliminate a infectious sclerites
  - nodular and diffuse scleritis

    in the absence of an Associated autoimmune disease
    in treatment resistance (NSAIDs and general corticoids) with progression towards ischemia and necrosis.

Anterior Primary Scleritis

Symptoms

- moderate to severe eye pain, deep, irradiated to the face, cheek, sharpened at night and with eye movements (more pronounced pain in hzv scleritis, more severe in idiopathic scleritis)
- photophobia, lacrimation
- decreased vision depending on the location of scleritis

Clinical

- red eye with localised purplish conjunctival hyperaemia
- scleral node in single or multiple palpebral cleft with vascular congestion intense damage to the deep vascular plexus (Fig. 6.1)
- thinning of the sclera with evolutionary necrosis, with intense pain until perforation
- bluish sclera in necrotizing anterior scleritis

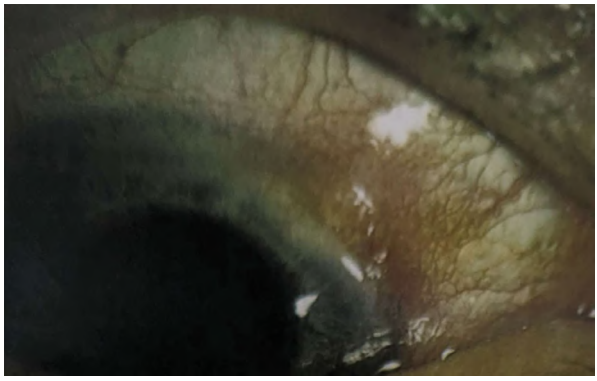

Fig. 6.1 Limbic nodular scleritis

Diffuse Anterior Scleritis

- 40% benign with inflammation in an anterior sector of the sclera
- the most common form
- accompanies with dilatation of the vascular plexus, deep sectoral or diffuse
- purplish hyperaemia in the interbalpebral area

Nodular Scleritis

- 44% presence of 1–2 Immobile, prominent nodules, located 2–3 mm from limb, with circumscribed inflammation
- palpable, single or multiple nodules in the interbalpebral space
- red nodules uninfluenced by local vasoconstrictors
- nodules near the limb, sometimes arranged annularly perilimbic

Necrotizing Scleritis with Inflammation

- rare, severe form with intense localized inflammation, with thinning of the Selera by tissue necrosis, sometimes accompanied by scleral ectasia, with uvea herniation (tissue necrosis is accompanied by intense pain);
- progressive focal or diffuse scleritis with red, painful eyes, 40% decreased AV
- severe form, evolves with ischemia accompanied by progressive necrosis with thinning of the sclera
- sclera with a brownish-gray area, is surrounded by scleral inflammation, zone which becomes avascular and produces white dot in the center surrounded by a dark circle
- rapid progression (week) to scleral perforation
- in the favorable course under treatment sclera remains thin and scleritis is accompanied by eye complications: uveitis, keratitis, cataract, glaucoma
- it is present in Wegener's granulomatosis and rheumatoid periarteritis

Necrotizing Scleritis Without Inflammation

Scleromalacia perforans—extremely rare, serious, associated with severe rheumatoid arthritis or nodular periarthritis.

- more common in women, with 20% mortality rate in 8 years
- symptoms-often asymptomatic without pain, without inflammatory signs
- clinical
  - asymptomatic scleral necrosis with thinned sclera and visibility choroid with scleromalacia perforans
  - begins as an evolving necrotic yellow spot in the sclera the sclera thins, with the visibility of the underlying choroid
  - evolves with important ischemia
  - scleromalacia is related to a degenerative necrotic process of the sclera
  - in the presence of HTIO sclera can perforate and uvea hernias

Posterior Primary Scleritis

Presents scleral inflammation behind the equator, unilateral, very painful [2].

Symptoms

- intense eye pain accentuated on eye movements with irradiation to forehead, jaw, sinuses, Awakens the sick person from sleep and is exacerbated at touch
- decreased AV, most commonly by complications
- photophobia
- diplopia by motility disorders
- ptosis
- proptosis

Clinical

- white eye, conjunctival chemosis, proptosis, eye oedema
- indirect retinal signs: choroid folds, retinal, papillary edema, DR exudative, increased IOP
- ophthalmoplegia
- blepharoptosis

Complications

- sclerokeratite
- sclerouveite
- glaucoma 10–15% (cortisone-induced and angle-closure glaucoma)
- cataract
- papillary, macular, DR exudative oedema

Differential diagnosis of posterior scleritis

- DRR
- choroid tumors
- inflammatory pathology of the orbit
- Uveal Effusion Syndrome
- intraocular lymphoma

Treatment [3]

- Interdisciplinary therapeutic attitude ophthalmologist, internist, rheumatologist, infectious diseases
- Treatment objectives [6]:
  - pain control
  - limitation of relapses, ocular and general complications
  - etiological treatment (if detected)

Local treatment-is indicated in forms of episcleritis, anterior scleritis

- artificial tears
- NSAIDs topical: Indocid, Diclofenac, Ketorolac 1 pic 4/day
- Topical corticoids 1 pic 5/day: prednisolone 0.5%, prednisolone acetate 1%, Dexamethasone 0.1%, Betamethasone 0.1%

Systemic Medical Treatment

- Systemic NSAIDS is the first line of treatment for forms of nonnecrotizing scleritis
- Ibuprofen 800 mg 3/day
- Indocid 75 mg 2/day
- Naproxen 500 mg 3/day
- Corticoids indicated in severe forms of necrotizing scleritis
  - Prednisone-oral 1 mg/kg/day with progressive dose reduction and gastric protection (omeprazole)
  - Injectable steroids: i.v., I.m., subconjunctival (with great care because sclera can perforate). **Subconjunctival steroids contraindicated in necrotizing forms.**
- Immunosuppressive agents-indicated in severe forms of scleritis
  - Cyclophosphamide-of choice in necrotizing sclerites-1–3 mg/kg/day orally
  - Methotrexate 7.5–1.5 mg/week-of choice in non-necrotizing sclerites agents that do not respond to NSAIDs
  - Azathioprine
  - Cyclosporine
- Immunomodulators if the therapeutic response is weak to immunosuppressants—Infliximab
- Systemic antibiotics in infectious sclerites
- Surgical treatment—Scleral graft under perforation conditions

Treatment in diffuse or nodular non-necrotizing anterior scleritis

- Topic
  - dexametaxon by the hour, with a gradual decrease in the rate of administration
  - NSAIDs
  - Atropine
- Oral
  - NSAIDs
  - Prednisolone 40 80 mg/day in resistant cases
  - Combination of NSAIDs with low doses of corticoids
- subconjunctival-cautious (alternative to general treatment, triamcinolone 40 mg/ml)

Treatment in anterior necrotizing scleritis with inflammation

- Contraindicated local injection of corticoids for the danger of globe piercing
- Prednisolone 60–100 mg/day with progressive decrease
- Immunosuppressants-cyclophosphamide, azathioprin, cyclosporin in corticoresistant cases
- Combinations, immunosuppressants-cyclophosphamide 500 mg and corticoids—methylprednisolone 500–1000 mg in scleral necrosis or resistant to oral treatment

Treatment in anterior necrotizing scleritis without inflammation—scleromalacia perforans—immunosuppressants.

Treatment in posterior scleritis

- elderly patients-same treatment as previous necrotizing scleritis
- **in young people without systemic pathology-NSAIDs**

Surgical treatment—if necessary

- surgical resection in the ulcerated area
- amniotic membrane graft
- lamellar corneal transplantation
- scleral graft in scleral perforation

Episcleritis and scleritis secondary to inflammation and eye infection

- Secondary scleral or episcleral inflammation is associated with extension to sclera of inflammatory lesions from conjunctiva, cornea,uvea (intermediate more common), surgical or accidental trauma of the eyeball, intraocular necrotizing tumors. Sclera can also be affected by the propagation of infection from neighboring structures: sinuses, orbit.

***Blue Sclera, osteognesis imperfecta*—LOBSTEIN'S DISEASE**

Table 6.3 Classification of imperfect osteogenesis

Type I	Type II	Type III	Type IV
–AD –Blue sclera –Bone fragility –Decreased hearing	–AD, AR, mutations –The most severe form presents at birth (can be lethal) –Blue sclera –Bone deformities, multiple fractures that appear in childhood and decrease in adolescence	–AD with penetration, variable AR –Childhood Blue sclera	–Childhood Blue sclera –Normal sclera in adulthood

- A thin bluish sclera associated with osteogenesis is present imperfect
- Other causes: Marfan syndrome, Ehler Danlos, buphthalmic elastic pseudoxanthoma, myopia forte, sclerites with scarring and scleral thinning, Streiff syndrome, Albright
- The thin Sclera is bluish and allows visibility of the uvea (in adult sclera it is gray)
- Lobstein's disease—osteogenesis imperfecta presents:
  - sclera light blue
  - fragile vessels
  - decreased presenil hearing

Classification of imperfect osteogenesis (Table 6.3).

Scleral thinning in buphthalmia.

Sclera pachynsis—bilateral thickening localized to the internal 2/3 of the sclera posterior temporal that compresses the choroid and macula.

Acquired Abnormalities of the Sclera

Scleral staph

- Is a scleral bulge located at the level of the external tunic of the eye, cornea and / or sclera that are thinned with uvea visibility
- develops after traumatic, inflammatory injuries, intraocular hypertonia
- Anatomically scleral staph is:
  - **Anterior** near limbo
  - intercalary

    localized to the limb after peripheral corneal ulcer, associated with glaucoma closed-angle secondary
    important vision defect due to corneal astigmatism
    ciliary
    located 2–3 mm from the limb, next to the ciliary body
    develops after perforating wounds, sclerites, absolute glaucoma
  - Equatorial

in the area where the sclera is perforated by the vorticous veins, in the bulging choroid
is present in sclerites, pathological myopia

– posterior located behind the equator, is present in myopia degenerative, posterior scleritis, perforating wounds.

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Chapter 7
Ophthalmological Pathology and Management in Eye Disease: Cornea

Marieta Dumitrache

Abstract **Corneal dystrophies** are non-inflammatory, bilateral, progressive, frequently symmetric, genetic disorders, associated or not with systemic diseases. **Corneal dystrophies are anterior** (Cogan, Meesman, Reisbucklers), stromal (Biber, Haab-Dimmer, Schneiner, Groenow I, II) and posterior (cornea guttata, Fuchs endothelial dystrophy). **Corneal degenerations** that can be related to age. **Infectious inflammatory diseases of the cornea, keratitis** be ulcerative—corneal ulcer and superficial or deep non-ulcerative**, and suppurative corneal abscess, central or peripheral.** Superficial ulcerative bacterial keratitis, represented by **corneal ulcer, central or marginal**, Corneal ulceration has a staged evolution, with the extension of the ulceration in the surface and depth of the cornea, with possible the stage of descemetocele, which may perforate and which may be accompanied by complications: adherent corneal leukoma, secondary glaucoma, uveitis, endophthalmitis, various corneal scars. Corneal ulcer treatment requires antibiotics systemic adapted to the offending bacteria, and locally administered antibiotic. **HSV viral keratitis** has multiple clinical forms: epithelial, stromal and possibly keratouveitis. The treatment of herpetic keratitis is with local antivirals and systemic, **Fungal keratitis** can be. **Deep stromal keratitis** is of specific bacterial etiology (syphilis, TB, leprosy), or viral HSV, Epstein-Barr virus. **Keratitis can be immune-mediated** in corneal diseases associated with rheumatoid arthritis or collagen diseases (polymyositis, dermatomyositis, Wegener's granulomatosis, Behcet's). **Emergencies in corneal pathology** present in corneal abrasion, corneal foreign body, chemical burns (acid, bases), thermal burns.

Keywords Corneal dystrophies · Corneal degenerations · Keratitis · Corneal ulcer · Ulcerative or non-ulcerative keratitis · Superficial or deep corneal ulceration Tarsorrhaphy · Corneal graft · Descemetocele · HSV viral keratitis · Corneal foreign body · Corneal burns

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- The cornea is a transparent, avascular membrane with a refractive power of around 45 diopters (the total refraction of the eye is 60 diopters).
  - the anterior surface of the cornea is elliptical, has a horizontal diameter of 11.7 mm and a vertical diameter of 11 mm;
  - the posterior surface of the cornea is circular, with a diameter of 11 mm;
  - the thickness of the cornea is 0.52 mm, and in the periphery, it is 0.7 mm;
  - the 5 mm central area of the cornea forms the refractive surface of the eye.
- Keratitis is an inflammation of the cornea that can be dystrophic, degenerative, infectious inflammatory central or peripheral, epithelial or stromal, some immune-mediated, neurokeratopathies or metabolic keratopathies.
- Keratitis is related to damage to the corneal epithelium and stroma through the inflammatory reaction produced by infectious agents: bacteria, viruses, fungi.

Deposits on the Surface of the Cornea

Superficial

Band Keratopathy

- Calcium deposits in the basement membrane of the Bowman's epithelium and the anterior stroma, located interpalpebrally [1];
  - Causes:

    hypercalcemia in hyperparathyroidism
    chronic eye inflammations—chronic uveitis, chronic corneal edema, glaucoma
    autoimmune inflammations—juvenile rheumatoid arthritis
    diseases with genetic transmission: Still's disease, Norrie's disease, ichthyosis, tuberous sclerosis
    systemic diseases—multiple myeloma, sarcoidosis, uremia
    idiopathic
- Clinically—opaque band in the interpalpebral area with onset in the periphery and progressive extension towards the center
- Treatment—chelating agents

Iron Deposits

- Yellow-brown line in the epithelium
  - Hudson-Stahli line—interpalpebrally
  - Stocker's line—at the head of the pterygium
  - Ferry line—adjacent to the filter bubble

  - Fleisher's ring—the base of the cone in keratoconus
  - Mannis line—at the base of the suture in the corneal graft

Cornea Verticillata

- Linear opacities in the corneal epithelium in [2]:
- Sphingolipidoses
- ARX present in heterozygous females and homozygous males
- by galactosidase deficiency
- clinically—cornea verticillata and cataract with wheel spoke-like opacities
- angiokeratome, heart, kidney, brain abnormalities
  - patients under systemic treatment with: amiodarone, chlorpromazine, chloroquine, indocid

Fluoroquinolone Deposits

- Chalky white precipitates by ciprofloxacin, norfloxacin

Ochronosis (Alkaptonuria)

- Melanin-like pigment deposits in the epithelium and superficial stroma

Tyrosinemia

- Linear or branched opacities, bilateral, sometimes similar to HSV dendrites.

Stromal

Blood Deposits

- They are present in the hyphema, initially as small yellowish granules in the posterior stroma.
- Red deposits in persistent hyphema

Bilirubin

- Deposits in the periphery of the cornea, protrusions in the posterior stroma.
- They are associated with conjunctival bilirubin deposits in liver disease (cirrhosis) or biliary obstruction.

Siderosis

- Iron deposits in the ocular structures in the presence of an intraocular iron foreign body or in systemic diseases (hemochromatosis).

Lipid Deposits

- *Arcus senilis* is the most common lipid deposit in the corneal periphery with initial superior and inferior onset with circumferential emergence
  - -the deposits are greyish-white rings separated from the limbus by a free space
  - -lipid degeneration can be: primary not associated with lipid increase or secondary in corneal neovascularization, interstitial keratitis, corneal ulcer (when lipid deposits are finer).

Immunological Deposits

- Present in systemic diseases: primary in amyloidosis, multiple myeloma, Waldenstrom macroglobulinemia, lymphoma, crystals being often the initial sign of the disease.

Cystinosis

- Crystals deposited in the anterior stroma with extension into the surface of the cornea, iris, lens, retina, accompanied, in severe forms, by photophobia and recurrent erosions.
- Clinical forms: infantile—Fanconi syndrome with: polyuria, growth retardation, progressive renal failure, "salt and pepper" fundus, death before puberty; in teenagers, less severe, AR, in adults—limited deposits in the anterior segment.
- Treatment–topical, systemic cysteamine

Kayser-Fleisher Ring

- It is caused by copper deposits in the basal ganglia (spasticity, dysarthria, tremor, ataxia), in the liver (cirrhosis), in eyes, where copper is deposited in the deep stroma and in the periphery of the superior and inferior Descemet's membrane medially and temporally and sunflower cataract.
- The Kayser-Fleisher ring is present in the Wilson's disease—AR hepatolenticular degeneration.
- Treatment—penicillamine

Chrysiasis

- Gold deposit in the form of yellowish-brown granules at the level of the Descemet's membrane, asymptomatic, in patients under treatment with gold salts in rheumatoid arthritis.

Cornea Farinata

- Multiple whitish opacities, bilaterally in the posterior stroma.

Changes in Ocular Surface

They are produced by disruptions of the tear film and dry eye. Tear film and dry eye disorders are generated by deficiencies in the composition of the tear film [3].

- **Deficiency of the aqueous component**
- It is generated by:
  - lacrimal gland dysfunctions—aplasia—surgical removal
  - infiltrations—sarcoidosis, thyroid disease, lymphoma, amyloidosis
  - inflammations: mumps, Sjögren's syndrome
  - idiopathic congenital or acquired Riley-Day familial dysautonomia (Shy Drager syndrome)
  - Möbius syndrome
  - drugs that decrease tear secretion (antihistamines, diuretics, anticholinergics, psychotropic medication)

Keratoconjunctivitis sicca **is the clinical manifestation of the deficient aqueous component of the tear film.**

Sjögren's Syndrome

Clinically, it presents:

- keratoconjunctivitis sicca
  - xerostomia by decreasing the parotid secretion flow
  - lymphocytic infiltration of the salivary glands
  - positive ANA test, rheumatoid factor, HLA–B8 (90%)
  - Symptoms: foreign body sensation, burning, tearing, dry eyes.

Mikulicz Syndrome

- Hypertrophy of the lacrimal gland and keratoconjunctivitis sicca in: sarcoidosis, TB, lymphoma, leukemia

Tear Film Mucin Deficiency

Causes of the mucin deficiencies are:

- **Xerophtalmia**
- It is an epithelial keratinization produced by vitamin A deficiency through: chronic liver dysfunction, cystic fibrosis and poor diet (alcoholics).
- Clinically: nyctalopia (decreased night vision), conjunctival dryness, Bitot's spots, corneal dryness with ulcerations and keratomalacia, scars.
- **Stevens-Johnson syndrome**
- It is present in young people, with 25% recurrence, 33% mortality.
- Etiologically, it is caused by: infections (HSV, mycoplasma), idiopathic, drugs (sulfamides, antibiotics, barbiturates, phenytoin).
- Clinically:
  - pseudomembranous conjunctivitis, symblepharon, dry eye, trichiasis, erosions, corneal ulcer, corneal neovascularization
  - sometimes erythema multiforme with bullous rashes, facial rash, mucosal ulcerations, fever, athralgias.
- Treatment—steroids, lubricants, avoidance of symblepharon.
- **Ocular cicatricial pemphigoid**
- It is a disease of the mucous membranes with a bullous appearance, followed by scarring, of autoimmune etiology in people >60 years old, associated with HLA–B12 and drugs (pilocarpine, thymol, epinephrine, idoxyuridine).
- Clinically:
  - symblepharon, ankyloblepharon, trichiasis, entropion, dry eye, corneal ulcer, neovascularization, scarring.
  - vesiculobullous lesions on the skin in the groin region, extremities, scalp, face and mucous membranes–nose, pharynx, larynx, esophagus with stricture, dysphagia.
  - Treatment:
  - immunosuppressive, dapsone, cyclophosphamide, surgical treatment
  - limited keratoprosthesis in advanced stages

Lipid Deficiency

It is produced by diseases of the Meibomius gland in blepharitis, meibomitis, acne rosacea

- **Acne rosacea**
- It is a chronic oculodermal condition with granulomatous inflammation in which the sebaceous glands of the face (including the Meibomian glands) are affected; it is present at the age of 40–60.
- Clinically:
  - chronic blepharitis, meibomitis, thalangiectasia—on the edge of the eyelids, conjunctival hyperemia, tear film abnormalities, recurrent chalazion, peripheral corneal infiltrate, rarely ulcer
  - skin changes with papillae, telangiectatic vessels, rhinophyma.
  - Treatment:
  - Warm compresses, antibiotic ointment
- Systemically:
  - doxycycline, erythromycin, metronidazole
- **Other factors** that contribute to disruption of the tear film:
  - Increased evaporation: lagophthalmos, Bell's palsy, ectropion, entropion, thyroid ophthalmopathy
  - Treatment—Tarsorrhaphy

Transparency Anomalies of the Cornea

- They are present in: corneal edema, corneal dryness, inflammations, dystrophies, degenerations, vascularization, corneal opacities.

Corneal Edema

Corneal edema occurs when the normal water content (78% in the cornea) increases, which causes a reduction in corneal transparency.

- Causes of corneal edema:
  - increase in IOP
  - damage to the epithelium by mechanical damage, chemical burns, radiation
  - damage to the endothelium by:

inflammations in: uveitis, endophthalmitis, corneal ulcer
dystrophies: Fuchs, posterior endothelial dystrophy
trauma (forceps, contusions, wounds) surgical interventions.

- Clinically:
  - initially stromal imbibition with visual acuity reduction
  - in evolution, permanent edema with vesicles and epithelial bubbles (bullous keratopathy) with large decrease in visual acuity, pain, photophobia at the time of bubble rupture and/or chronic endothelial damage (Fuchs' dystrophy).
- Treatment:
  - causal treatment of inflammation, of intraocular hypertension
  - dehydration of the cornea—hypertonic agents–sodium chloride eye drops, ointment
  - therapeutic contact lenses for bullous keratitis
  - penetrating keratoplasty.

Corneal Opacities

- Corneal opacities are the loss of normal transparency of the cornea.
- Clinical forms:
- Corneal opacities are the loss of normal transparency of the cornea.
- Clinical forms:
  - nebular corneal opacity –it affects the Bowman's membrane and the superficial stroma; can produce visual acuity damage (if centrally located) and irregular astigmatism
  - larger macular corneal opacity, produces visual acuity changes if it is central
  - leukomatous corneal opacity–simple leukoma, variable sizes, single, multiple
  - adherent leukoma–after corneal perforation with iris incarceration
  - opaque corneal ectasia with changes in corneal curvatures
  - anterior staphyloma—ectatic swelling of the anterior pole of the cornea.
- Corneal opacities can sometimes be vascularized when deep keratitis has a chronic relapsing course or in specific etiologies (HSV, rosacea, chemical burns etc.).
- Treatment:
  - optical iridectomy–when the opacity is central
  - keratoplasty—in cases of uncomplicated opacity
  - excimer laser phototherapeutic keratectomy in superficial opacity
  - aesthetic staining of leukoma
  - tattooing

Corneal Neovascularization

- Normally, the cornea is avascular except for a 1 mm area in the limbic periphery.
- In pathological conditions, in various eye diseases, neovascularization occurs that disturbs the transparency of the cornea and can cause corneal irritation.

Superficial Corneal Vascularization

– represents vessels located in the epithelial layer
– can be in continuation of the conjunctival vessels
– has an arborescent disposition
– etiology: trachoma, phlyctenular keratoconjunctivitis, superficial corneal ulcer, rosacea keratitis
– ***pannus*** in which superficial vasculature is associated with cellular infiltration.

Deep Corneal Vascularization

– the vessels derive from the anterior ciliary artery and reach the stroma
– strong, non-anastomosed vessels that can continue beyond the limbus
– the vessels have different aspects: arborescent, bundle-like, brush-like appearance, being able to produce interstitial arches
– etiology: interstitial keratitis, disciform keratitis, deep ulcer, chemical burn, sclerosing keratitis, corneal graft.

Treatment:
- unsatisfactory
- preventive:
  – appropriate causal treatment
  – corticosteroids
  – more effective irradiation in the superficial vasculature
  – surgical—peritomy for superficial vessels

Corneal Dystrophy

They are non-inflammatory, bilateral, progressive, frequently symmetric conditions, with genetic transmission, associated or NOT with systemic diseases [4].

Anterior Corneal Dystrophies

Cogan dystrophy—microcystic (map-dot-fingerprint)
- AD dystrophy, bilateral, symmetric, central with onset at the age of 8
- linear, punctate, microcystic, map-dot-fingerprint opacities; more visible in backlight, with minimal impairment of the visual acuity;
- produces recurrent painful corneal erosions (on waking) precipitated by trauma
- Treatment
  - of recurrent erosions: topical sodium chloride 5%, artificial tears, therapeutic contact lenses
  - debridement of the epithelium, anterior stromal puncture
  - excimer laser phototherapeutic keratectomy

Meessmann dystrophy
- bilateral, symmetric, non-evolving, asymptomatic AD dystrophy in children
- under the biomicroscope, small, multiple intraepithelial cysts, visible under backlight, which may merge; in evaluation, syndrome of painful recurrent erosions;
- Treatment
  - similar to Cogan dystrophy
  - lamellar or perforating keratoplasty if needed

Reis-Bücklers dystrophy
- AD condition, symmetrical, central, bilateral, symptomatic in childhood, with episodes of recurrent corneal erosions with pain, lacrimation, photophobia
- central, white/grey reticular subepithelial opacities with progressive decrease in visual acuity
- Treatment
  - of episodes of recurrent corneal erosions
  - phototherapeutic keratectomy
  - lamellar keratoplasty, perforating, with graft recurrence.

Corneal stromal dystrophies [5]

Reticular dystrophy (lattice dystrophy) Biber Haab-Dimmer
- AD (type 1) AR (type 2) with onset in the first 10 years of life, with recurrent corneal erosions, by amyloid deposition in the stroma
- white subepithelial opacities in the anterior stroma, central, punctate and linear, in the advanced stage they thicken, become radial and the cornea appears as a frosted glass
- decrease in visual acuity due to irregular astigmatism
- clinical forms:

  - type 1–Biber Haab-Dimmer syndrome without systemic involvement
  - type 2—Meretoja syndrome associated with systemic amyloidosis with peripheral polyneuropathy, skin lesions, renal, cardiac amyloidosis
  - type 3—amyloid deposits in the periphery of the cornea, decrease in visual acuity

- Treatment
- of recurrent corneal erosion syndrome
- perforating keratoplasty with graft recurrence

Central crystalline dystrophy—Schnyder
- AD, bilateral, central condition with deposition of cholesterol crystals in the anterior stroma.
- Central corneal opacity, well demarcated with polychromatic crystals
- (+ gerontoxon, Vogt ring)
- Initially asymptomatic, it may evolve with slow visual acuity decline
- Treatment:
  - Perforating keratoplasty in severe opacities

Granular dystrophy—Groenouw I
- AD condition, with hyaline degeneration in the anterior stroma, the **most common form of stromal dystrophy**
- decreased visual acuity by white/gray, granular opacities in the anterior stroma, separated by clear areas, with a tendency to confluence and extend in depth and surface, stopping 2–3 mm from the limbus
- onset in childhood, asymptomatic, rarely recurrent erosions
- treatment:
  - rarely, lubricants, contact lenses are needed for recurrent erosions
  - lamellar or perforating keratoplasty if needed

Macular dystrophy—Groenouw II
- AR condition, by accumulation of keratan sulfate (localized mucopolysaccharidosis) in the anterior stroma, with onset in the first 10 years
- **it is the most common stromal dystrophy and the most severe**
- central superficial white/gray stromal opacities with deep and peripheral progression; associated with cornea guttata
- rarely episodes of recurrent erosions
- decrease in visual acuity after the age of 30

The treatment depends on the symptomatology and clinical evolution with: reduction of photophobia (colored lenses), treatment of recurrent erosions with contact lenses, lubricants, lamellar or perforating keratoplasty if needed.

Avellino dystrophy
- AD, combines granular opacities in the superficial stroma with reticular opacities in the deep stroma; combination of granular and lattice
- Episodes of recurrent erosion

- Treatment—contact lenses, keratoplasty if needed
- Good prognosis

Endothelial Posterior Corneal Dystrophies

- Bilateral, asymmetric, noninflammatory, edematous condition with corneal opacities at birth and endothelial dysfunction with protrusions (round, teardrop, mushroom-like) of Descemet membrane and endothelium by dystrophic endothelial cells

Cornea gutatta
- In the advanced forms, "beaten metal" appearance
- Patients operated for cataract with cornea gutatta may have transient corneal edema for several weeks
- 10% may have Fuchs' endothelial dystrophy (corneal edema with cornea gutatta)
- Variable prognosis
- Treatment—perforating keratoplasty

Fuchs' endothelial dystrophy
- **It is the most common bilateral endothelial dystrophy,** AD, asymmetric and progressive through the synthesis of abnormal collagen resulting in thickening of Descemet's membrane, more common in older women.
- Symptoms: blurred vision on waking, pain over time through recurrent erosions
- Staged evolution:
  - stromal and epithelial edema with microcystic corneal thickening, subepithelial bullae (bullous keratopathy) that tear and cause episodes of pain upon awakening
  - cornea gutatta (protrusions) at Descemet's membrane level
  - subepithelial fibrosis
- Treatment:
- pain reduction:
  - therapeutic contact lenses
  - conjunctival covering
- Reduction of corneal edema
  - sodium chloride 5% × 4/day, ointment in the evening
  - artificial tears
  - hair dryer in the morning
  - perforating keratoplasty

Corneal Degenerations

- **Corneal degenerations according to location** [6]
  - axial

    fatty, hyaline degeneration, amyloidosis
    calcific—band keratopathy
    Salzmann's Nodular Degeneration

  - peripheral

    senile arch
    Hassal-Henle bodies
    Terrien degeneration
    Mooren's ulcer
    pellucid marginal degeneration
    senile furrow degeneration

- **Corneal degenerations by etiology**
  - age-related degenerations: senile arch, Vogt, Hassal-Henle, mosaic degeneration
  - pathological degenerations: fatty, calcific, amyloidosis, pellucid, Salzmann's, Terrien, Mooren.

Age-Related Degeneration

Senile arch
- Senile arch is an annular lipid infiltration of the peripheral cornea, bilateral, occurring at the ages of 40–60 (60%) and very common after 80 years old (*arcus juvenilis* may or may not be associated with hyperlipidemia).
- It starts from the upper and lower quadrant progressively circumferentially in a ring shape of around 1 mm, the ring being an opacity separated from the limbus by a clear zone—(Vogt interval); sometimes it can be a double arch ring

Vogt's limbal girdle
- White spots, bilaterally, along the nasal and temporal limbus.

Cornea farinata
- Bilateral deep stromal flocculent deposits, predominantly central.

Crocodile skin
- Stromal opacities, bilateral, polygonal, poorly marked, separated by clear areas.

Hassal-Henle bodies
- There are growths of hyaline material projected from anterior chamber around the periphery of the cornea signs of senile or pathological changes in the cornea gutatta.

Pathological Degenerations

Lipoid (fatty) degeneration
- It can be idiopathic without neovascularization or secondary to a chronic corneal pathology and then, it is associated with neovascularization (in interstitial keratitis, trauma, glaucoma, chronic iridocyclitis).
- Signs—yellowish deposits located superficially in the corneal stroma consisting of cholesterol and phospholipids that can produce stromal cell necrosis.
- Treatment:
  - argon laser photocoagulation can promote lipid resorption
  - localized cauterization
  - cornea graft

Hyaline degeneration
- Deposits of superficial hyaline spherules in primary stroma, bilaterally, associated with granular dystrophy or secondary, unilaterally associated with keratitis, glaucoma, trachomatous pannus complicated with recurrent corneal erosions.
- Treatment:
  - causal
  - keratoplasty, if needed

Amyloid degeneration
- It is characterized by amyloid deposits in primary, secondary epithelium.

Cornea verticillata
- Bilateral brown epithelial deposits, after the use of drugs (chloroquine, amiodarone, Fabry disease).

Kayser-Fleischer ring
- Yellow/brown or yellow/green corneal ring due to copper deposit in Descemet's membrane in Wilson's disease (liver and lens damage).

Calcific band keratopathy
- It is a degeneration produced by calcium deposits in Bowman's membrane, superficial stroma, and epithelium in interpalpebral space, with clear limbic region.

Spheroidal Degeneration

- It is present in individuals exposed to UV
- Clinically:
  - superficial, brown, bilateral, interpalpebral stromal nodules
  - brown drops on the conjunctiva
- Treatment:
  - sun protection with glasses
  - superficial keratectomy
  - lamellar keratoplasty

Salzmann's nodular degeneration
- It is secondary to chronic keratitis: phlyctenular, rosacea, trachoma, more common in women, unilateral
- Hyaline plaques are present and are deposited between Bowman's membrane and epithelium, followed by destruction of Bowman's membrane and stroma
- Clinically:
  - gray-white nodular opacities (bumps), arranged circularly, accompanied by eye discomfort
  - decrease in visual acuity if nodules affect the central area

Terrien's marginal degeneration
- Peripheral corneal inflammation (rare) after the age of 40, more common in men, bilateral, asymmetric, with slow evolution.

Corneal Ectasias

Keratoconus

- Keratoconus is a non-inflammatory, bilateral (85% of cases), progressive, paracentral, axial corneal dystrophy manifested by a central conical ectasia of the cornea due to progressive thinning of the stroma with a cone tip in the visual axis, probably genetic, with onset at puberty and slow progressive evolution [6].
- Initially asymptomatic, the diagnosis is established at puberty by intermittent, minimal visual disturbances, then pronounced and permanent with **decreased visual acuity by myopia and astigmatism.**
- Clinically:
  - irregular corneal astigmatism, difficult to correct

- the accentuation of the corneal curves, which generate from the normal sphericity of the cornea, a slightly off-centered conical curvature, more accentuated downwards
- Fleisher ring—stromal thinning of the cornea near the central and paracentral conical deformation through apical protrusion
- Vogt's striae—sequellae of corneal opacities after episodes of parenchymal edema
- acute hydrops with deep corneal edema with sudden opacification of the cornea, with the presence of aqueous humour in the cornea, with Munson's sign (deformation of the lower eyelid when looking down)
- acute hydrops does NOT perforate except in the presence of trauma or under steroid treatment
- keratoplasty is NOT indicated in acute hydrops

Complications:

- acute keratoconus
- it is an evolutionary accident produced by rupture of the Descemet's membrane and hydrops with massive edema in keratoconus
- brutal and massive drop in visual acuity, eye pain, lacrimation, photophobia
- possible regression in a few days with leucomatous corneal opacity
- systemic associations: trisomy 21, Turner, Ehlers—Danlos, Marfan, atopy, osteogenesis imperfecta, mitral valve prolapse
- ocular associations—vernal keratoconjunctivitis, blue sclera, aniridia, crystalline ectopy, congenital cataract, Leber congenital amaurosis, RP.

Treatment:

- optical correction in early forms for the correction of myopia or myopic astigmatism
- rigid, gas permeable contact lenses for the correction of irregular astigmatism
- surgical, when the cornea is very thin, with scars and the astigmatism is very severe
- perforating keratoplasty, intrastromal rings at the level of the cornea with temporary stabilization
- excimer laser for eccentric elevation correction (counter-indicated if there is no topographic progression)
- cross-linking may be beneficial to prevent disease progression

Treatment of acute corneal hydrops

- cyclogyl, scopolamine
- sodium chloride 5% for months × 2/day
- initial dressing

Pellucid Marginal Degeneration *(PMD)*

It is a peripheral corneal ectasia, bilateral with corneal thinning 1–2 mm, inducing significant astigmatism, located in the lower half of the cornea (from 4 to 8), with protrusion of the cornea in the thinned area, more common in men after the age of 40.

– it can coexist with keratoconus.

Clinically: irregular astigmatism with variable decrease in vision towards the age of 50

– lesions progress very slowly (over years) with thinning and superficial vascularization
– vision defects due to astigmatism

Complications:
• perforation upon minimal trauma
– pseudopterygium

Treatment
• Large diameter rigid contact lenses
– Lamellar keratoplasty, perforating if needed.

Keratoglobus

• Hereditary, familial, nonprogressive bilateral, AR congenital dystrophy with corneal thinning and globular protrusion of the center of cornea
• Ocular-associated conditions: Ehlers-Danlos syndrome, Leber congenital amaurosis
• Treatment:
  – correction of myopia, prevention of amblyopia
  – protection against trauma
  – perforating keratoplasty if needed (risk of corneal rupture)
• differential diagnosis: megalocornea, buphthalmia

Posterior Keratoconus

It is the internal protrusion of the curvature of the cornea, associated with thinning of the stroma, central or eccentric, sporadic, unilateral non-inflammatory, non-progressive, with various anomalies of mesodermal dysgenesis.

Treatment: requires correction of amblyopia and refractive errors.

Iridocorneal Endothelial Syndrome

- Unilateral, non-hereditary condition due to abnormalities of the corneal endothelium with slowly progressive evolution.
- Treatment:
  - lowering of intraocular pressure
  - surgical treatment of glaucoma if necessary
  - perforating keratoplasty if needed

Infectious Inflammatory Keratitis

Infectious inflammatory keratitis represents conditions located at the level of the cornea triggered and maintained by the inflammatory reaction produced by multiple infectious agents: bacteria, viruses, fungi characterized by edema, infiltrate, corneal ulcer and variable ciliary congestion depending on the virulence of the germs and the anatomo-functional status of the eye and body host

- Morphological classification of keratitis [7]
  - *ulcerative keratitis–corneal ulcer*—these have sub-classifications according to:

    location—central, peripheral
    purulent–suppurative-bacterial fungal ulcer
    non-purulent—viral, chlamydia, allergic
    associated or not with hypopyon
    depth: superficial, deep, with/without perforation

  - nonulcerative keratitis

    superficial

  - diffuse
  - punctate

    deep

  - nonsuppurative

    interstitial keratitis
    disciform keratitis
    deep keratitis
    sclerosing keratitis

  - suppurative

    central corneal abscess
    peripheral corneal abscess

- Etiological classification of infectious inflammatory keratitis

Bacterial Keratitis (Table 7.1)

The most common bacteria that cause keratitis are: *Staphylococcus aureus*, *Streptococcus pyogenes*, *S. pneumoniae*, *Pseudomonas aeruginosa* [8].

– Keratitis with intact corneal epithelium: Neisseria gonoreea, Corynebacterium difteriae, Listeria, Haemophilus
– Keratitis with corneal epithelial defect: stafilococ, streptococ, Pseudomonas [9–11]

- Risk factors
  - chronic pathology of the ocular surface: bullous keratopathy, neurotrophic keratitis
  - extended wear contact lenses
  - eyelid conditions (trichiasis, ectropion, lagophthalmia)—lacrimal conditions (dacryocystitis)
  - dry eye, blepharoconjunctivitis
  - systemic factors—diabetes, severe anemia, malnutrition, steroid treatment
- The clinical appearance is variable and is dependent on the virulence of the microorganisms, the duration of the infection, and the preexisting condition of the cornea [12].
- Symptoms—unilaterally
  - foreign body sensation
  - eye pain
  - photophobia
- Signs:
  - eyelid edema
  - perikeratic hyperemia
  - purulent discharge in bacterial infections, watery in viral ones
  - decrease in visual acuity
  - corneal infiltrate associated with stromal edema
  - sometimes hypopyon

Table 7.1 Bacterial keratitis—the most common etiology

Gram positive		Gram negative		
Cocci	Bacilli	Cocci	Bacilli	Coccobacilli
– *Staphylococcus aureus* – Staphylococcus coagulosis negative – *Streptococcus pneumoniae* and *viridans*	– *Corinebacterium* – *Propionibacterium* – *Micobacterium*	– *Neisseria*	– *Pseudomonas aeroginosa* – *Seratia marcescens* – *Proteus mirabilis* – *Enteric bacillus*	– *Hemofilus influenze* and *aegyptius* – *Moraxela*

  - corneal ulceration associated with corneal infiltration

- Laboratory examination—culture on:
  - Gelose/blood for most bacteria (no *Neisseria* and fungi)
  - Gelose/chocolate for *Neisseria, Haemophilus* and *Moraxella*
  - Gelose Sabouraud for fungi
  - Thioglycolate broth for aerobic and anaerobic bacteria

- Treatment:
  - locally:

    single-dose antibiotics (fluoroquinolones—Ciloxan), combined or fortified (aminosides, cephalosporins, vancomycins)
    instillations hourly for 48 h
    instillations every 2 h = 8–10 h
    duration of treatment: 2–4 weeks
    subconjunctival antibiotics if needed
    atropine
    corticosteroids after epithelization under strict medical check-up for 7–10 days.

- The negative response to antibiotic treatment is given by:
  - The pathogen resistant to the antibiotic used
  - Keratitis has another etiology (not bacterial), possibly HSV, fungi, Acanthamoeba, Nocardia, mycobacteria (very rare)

- Systemic and topical treatment with:
  - Antibiotic with a spectrum as close as possible to the nature of the bacterial agent
  - Fortified cephalosporins as needed—Cefazolin 15 mg/ml
  - Glycopeptides active on penicillin-resistant staphylococcus; vancomycin—fortified 25–30 mg/ml
  - Aminoglycosides active on *Pseudomonas Aeroginosa*: tobramycin, gentamicin, amikacin, netilmicin (fortified 14 mg/ml)
  - Macrolides—bacteriostatic and bactericidal depending on concentrations—active on gonorrhea, *N. meningitides*
  - Fluoroquinolones—active bactericidal activity on Gram—and some Gram + bacteria

- Surgical treatment
  - in extensive necrosis
  - emergency keratoplasty in descemetocele or perforated ulcer

Ulcerative Superficial Bacterial Keratitis

Bacterial Corneal Ulcer

Corneal ulcer—is a loss of substance that exceeds the superficial epithelial plane, with perilesional parenchymal edema; it is highlighted by green fluorescein staining.

Corneal ulcer is the expression of an infectious inflammatory process or the consequence of some neurotrophic disorders (in paralysis of the Vth cranial nerve—ophthalmic branch).

Causes of the Corneal Ulcer (Table 7.2)

Marginal Corneal Ulcer

Ophthalmological causes:

- Moore, Terrain, Pellucid marginal degeneration, Rosacea, Dry, severe keratoconjunctivitis, Neurotrophic keratitis, Exposure keratitis, Burns, Trichiasis, Palpebral deviations, Foreign body

Autoimmune: Sjögren, SLE, Wegener, rheumatoid arthritis, fibrosing conjunctivitis: pemphigoid, Lyell, Stevens Johnson.

Nonautoimmune: Diabetes, hemopathies, vitamin A deficiency, viral bacterial infections.

The corneal ulcer is produced by [13, 14]:

- damage to the corneal epithelium by corneal abrasion or foreign body, change in the position of the cilia, microtraumas, contact lenses, corneal dryness, exposure keratitis, bullous keratopathy with desquamation of the corneal epithelium, trophic in neuroparalytic keratitis

Table 7.2 Central corneal ulcer

Ophthalmological causes		
Mechanical	Infectious	Systemic causes
– Postoperative trauma – Cornea: foreign body, contact lenses – Corneal dryness syndrome – Neurotrophic ulcer—HSV, HZV, paresis of the Vth nerve – Exposure keratitis through VII paralysis, palpebral malposition – Epitheliotoxic eye drops: antiviral, aminosides, anesthetics – Epithelial, endothelial corneal dystrophy	– Bacteria – Viruses – Fungi – Parasites	– Collagenoses—rheumatoid polyarthritis – Allergies – Bacterial, viral infections

– exogenous (conjunctival, lacrimal sac, infected foreign body, burns) or endogenous bacterial superinfection
– germs that can produce corneal ulcer are (the most dangerous are *Pneumococcus* and *Pseudomonas*): *Staphylococcus*, *Pseudomonas*, *Streptococcus pneumoniae*, *Moraxella*, *E. coli*, *Proteus*, *Klebsiella*, *N. gonorrhoeae*, *N. meningitidis*, *C. diphteriae* (Table 7.3)

- Sources of infection
  – Exogenous infection: conjunctivitis, dacryocystitis, burns, corneal foreign body, environmental infections
  – Endogenous infection—rare because the cornea is avascular
  – From the ocular structures through anatomical continuity—sclera, uvea
- Stage-structure evolution
  – The stage of progressive infiltration
  – Stage of active ulceration with secondary epithelial necrosis and perforation that is dependent on bacterial clearance and host defense capacity
  – Regression stage of ulceration that may be accompanied by neovascularization
  – The stage of scarring with the progression of epithelialization and the organization of fibrous epithelium accomplishing corneal opacity, nephelioma, macula or leukoma (if the ulcer affects the stroma)
- Evolution of corneal perforation
  – Round corneal ulceration with hypertrophic infiltrated edges advances superficially and in depth to the Descemet's membrane, which bulges into the bot-

Table 7.3 The clinical appearance of corneal ulcers according to the nature of the bacterial agent [15]

Bacteria	Appearance of the infection	Treatment
Staphylococcus aureus epidermidis	– Slow progressive infection with minimal pain	Aminoglycosides, vancomycin
Streptococcus pneumoniae	– Oval ulceration surrounded by a relatively clear cornea, with dense white/yellowish deposit on the surface of the ulcer	Penicillins
Pseudomonas aeruginosa	– Ulcer with irregular borders with greenish purulent exudate, with diffuse necrosis, and semi-opaque cornea around the ulceration (ground glass appearance; the evolution of the ulceration is very rapid, with perforation in 48–72 h; extremely painful	Tobramycin
Moraxella	– Inferior corneal ulcer, slow progression	
Enterobacteria (*E. coli*, *Proteus*, *Klebsiella*)	– Superficial ulcer with greenish-white suppuration and diffuse stromal opalescence – The endotoxin of these gram bacteria—can produce annular corneal infiltrate	Cephalosporins

tom of the ulceration, being pushed by the intraocular pressure that presses on a resistant but thin membrane; it is the **descemetocele** stage—in this stage, minimal efforts (coughing, sneezing) favor corneal perforation. Immediately after the perforation, the aqueous humor drains, and the iris diaphragm advances towards the cornea, with the absence of the anterior chamber; when the ulcer perforates the patient feels a drop of warm water on the cheek, and the pain is reduced (or disappears).
  - The effects of perforation depend on the position and size of the perforation; if the perforation is small, the iris adheres to the base of the perforation and healing of the ulceration is rapid with **adherent corneal leukoma.**

- Symptoms:[12, 16]
  - eye pain, foreign body sensation
  - lacrimation (reflex)
  - photophobia
  - red eye with perikeratic congestion
- Signs:
  - eyelid edema
  - blepharospasm
  - conjunctival chemosis
  - oval, irregular corneal ulcer with marginal infiltrate extending in the surface and in depth with yellowish-white exudate on the surface of the ulcer
  - + sterile hypopyon in the anterior chamber if the Descement's membrane is intact
  - iris color changes
  - constricted pupil with posterior synechiae
  - increased intraocular pressure (inflammatory glaucoma)
- Complications
  - corneal leukoma
  - astigmatism
  - toxic iridocyclitis, acute uveitis with hypopyon
  - secondary inflammatory glaucoma
  - descemetocele–herniation of the Descemet's membrane by ulceration (prevents perforation) associated with intense pain that subsides after perforation
  - corneal perforation
- Sequelae of corneal perforation
  - iris prolapse after perforation
  - crystalline subluxation
  - anterior subcapsular cataract
  - corneal fistula
  - purulent uveitis
  - endophthalmitis

- corneal scars with corneal opacification and permanent visual acuity decrease: macula, leukoma, adherent leukoma
- corneal ectasia: anterior staphyloma
- The formation and evolution of the anterior staphyloma, which is a scar, occurs when the infectious agent is very virulent, the body's resistance is low and the associated fibrinoplastic iridociliary reaction blocks the pupillary opening.

- **Treatment of uncomplicated ulcers** [17, 18]
  - Treatment is causative specific and nonspecific supportive.
  - The goals of corneal ulcer treatment: limiting proliferation and eliminating the pathogen, reducing the destructive effects of the inflammatory infectious process, relieving pain
  - Antibiotics used in the treatment of bacterial keratitis[19]

- **aminoglycosides**
  - gentamicin, tobramycin—are active against staphylococcus and streptococcus except streptococcus pneumoniae
  - tobramycin against Pseudomonas aeraginosa

- **cephalosporins**—have an effect on the Gram+ cocci non-penicillinase producing and Gram bacilli—*Escherichia coli, Klebsiela, Proteus*
- **penicillins**—have an effect on streptococcus and *Neisseria*
- **vancomycin**—is antistaphylococcal
- **bacitracin and polymyxin**—inhibit *Clostridium perfringens, actinomyces*
- **Sulfonamides** are effective against *Haemophilus Nocardia*
  - Locally:

    Antibiotics by combining the therapy for Gram (+) and (−) (before culture result)
    Fortified antibiotics—gentamicin, tobramycin, cefazolin every 1/2 h on the first day, then every 2 h
    Cycloplegics—atropine
    Analgesic and anti-inflammatory

  - Generally—antibiotics–cephalosporin and aminoglycosides

- **Treatment of evolving ulcer** [20]
  - adequate treatment of risk factors
  - mechanical debridement of the ulcer with removal of necrotic material (with a spatula after local anesthesia)
  - eye patch or therapeutic contact lens
  - peritomy of perilimbic conjunctival vessels when there is excessive conjunctival vascularization
  - avoiding perforation

avoid coughing, sneezing
compressive dressing
intraocular pressure lowering with acetazolamide
mannitol 20%, thymol 0.5% or paracentesis
conjunctival covering
therapeutic contact lenses
penetrating keratoplasty (tectonic graft)

Perforated ulcer requires emergency keratoplasty [3, 10].

Medical Treatment of Bacterial Ulcer

The antibiotic is administered locally and generally according to the type of microbial agent and bacterial virulence.

Local treatment with:
- eye drops available in pharmacies: Fluoroquinolones (Norfloxacin, Ofloxacin, Ciprofloxacin), aminosides (Polymixin B, Gentamicin, Neomycin, Tobramycin, Gatifloxacin (Zimaxid), Moxifloxacin (Vigamox)
- reinforced eye drops prepared in the hospital: Vancomycin 50 mg/ml, Gentamicin 50 mg/ml, Cefazolin 50 mg/ml, Tobramycin 20 mg/ml.
- Etiological antibiotic treatment:
  - keratitis with gram (+) cocci: Cefuroxime
  - keratitis with gram (−) cocci: fluoroquinolone, ceftriaxone
  - keratitis with gram bacilli: Gentamicin, Fluoroquinolone
  - mycobacterial keratitis: amikacin, clarithromycin

Nonsteroidal anti-inflammatory drugs
- limit the non-specific inflammatory response

Topical and systemic *corticosteroids* **[21]**
- **must be associated with antibiotics administered topically 48–72 h before, in order to stabilize the infectious process: Moxifloxacin/Prednisolone**
- corticosteroids reduce inflammation, reduce neovascularization and stromal infiltration, favorably influence the healing process, reduce the risk of perforation

Cycloplegic and mydriatic eye drops—Atropine, 1%, Tropicamide.

Therapeutic contact lenses.

Anticollagenases—tetracycline and high-dose doxycycline reduce corneal ulceration by inhibiting collagenase.

Collagen cross linking—CXL—can be indicated in bacterial keratitis due to the potential to limit the enzymatic degradation at the level of the cornea.

Surgical treatment
- Tarsorrhaphy
- Amniotic membrane graft

- Corneal graft—lamellar, perforating, optical or therapeutic emergency keratoplasty

Treatment of corneal perforations
- small–contact lenses
- medium–tissue adhesive
- large, extensive, refractory to medical treatment require perforating keratoplasty

Conjunctival Flap Surgery in Peripheral Ulcers

Keratoprosthesis

Therapeutic management in corneal perforation
- Hospitalization
– Antibiotic therapy/protocol for endophthalmitis
– Peripheral and central perforated ulcer <2 mm—soft hydrophilic contact lenses or amniotic membrane graft >2 mm lamellar or transfixing keratoplasty

Corneal ulcer with hypopyon **[22] (Fig. 7.1)**
- Pyogenic bacteria—staphylococcus, streptococcus, gonococcus, Moraxella can produce hypopyon, **but the most dangerous is pyocyanic pseudomonas and pneumococcus (ulcus serpens).**
- The predisposing factors for the formation of hypopyon in patients with corneal ulcer are the virulence of the germs and the resistance of the organism; hypopyon ulcer is more common in elderly, alcoholic, immunosuppressed people.
– Corneal ulcer with hypopyon frequently located in the center of the cornea, is accompanied by severe acute iridocyclitis, with sterile hypopyon that rapidly increases in quantity and is often complicated by secondary glaucoma, frequently having a tendency to perforation.

Fig. 7.1 Corneal ulcer with hypopyon

Mycotic Corneal Ulcer

Fungi responsible for mycotic corneal ulcer are: aspergilus, candida, fusarium it can occur after a vegetative material or secondary trauma in systemically or locally immunosuppressed patients with dry eye, herpetic keratitis, bullous keratitis.

- The excessive use of antibiotics, corticosteroids, alters the saprophytic symbiosis and predisposes to fungal infections.
- Symptoms: similar to bacterial keratitis, but less important.
- Signs:
  - Onset with slower progression than bacterial keratitis
  - Gray stromal infiltrate and ulcer with slow evolution and satellite lesions with small clustered infiltrates and hypopyon
- **Identification of the germ by culture on Sabouraud and Chocolat agar**
- Treatment [23]
  - Topical—antimycotics—Natamycin, Nystatin, Amphotericin B (0.15%)
  - Systemic—antifungal—Voriconazole, Ketoconazole, 2–3 weeks in severe cases

Rosacea keratitis

- It is present in the clinical context of rosacea acne presenting simultaneously with lesions in the central area of the face (chronic inflammatory acne) and inflammation of the eyelids (chronic posterior blepharitis, palpebral telangiectasias (recurrent chalazion), conjunctiva (conjunctivitis, keratoconjunctivitis sicca) and cornea.
- Rosacea keratitis in its full form is a blepharoconjunctivitis associated with peripheral corneal thinning and neovascularization.
- Treatment:
  - Locally:

    Artificial tears
    Contact lenses
    Dexamethasone or Maxidex × 4/day
    Antibiotics—Fusidic acid, Azithromycin—ointment.
    Immunosuppressants—tacrolimus 0.03% × 2/day

  - Systemically:

    antibiotics:

    Doxycycline 100 mg/day the first month, then 50 mg/day for several months
    Erythromycin 250–400 mg × 4/day—1 month
    Azithromycin 500 mg/day

    Immunosuppressants—Azathioprine in refractory cases

Viral Keratites

- HSV is the most common cause of viral corneal ulcer by reactivation of latent HSV1, which migrates through the axon of the ophthalmic branch of the trigeminal nerve (V) to the cornea. Recurrence is influenced by external factors (UV exposure), internal factors: stress, immunological deficiencies, febrile infections [24].

Eye Lesions in Herpes [25]

HSV1—patients with herpes labialis.
HSV2—is transmitted to the eye of the newborn from the genitally infected mother.
HSV eye infection has two forms:

- Primary herpes
  - skin lesions
  - acute follicular conjunctivitis
  - cornea
    - epithelial punctate keratitis
    - dendritic ulcer
- Recurrent herpes
  - epithelial keratitis
  - punctate epithelial keratitis
    - dendritic ulcer
    - geographic ulcer
  - stromal keratitis
    - disciform keratitis
    - diffuse necrotizing stromal keratitis
  - trophic keratitis—metaherpetic
  - herpetic iridocyclitis
- Symptoms
  - intense eye pain associated with photophobia, lacrimation
  - decrease in vision acuity depending on the location of the ulceration

Clinical Forms of Herpetic Keratitis (Table 7.4)

Epithelial Keratitis [25]

- *Superficial punctate keratitis* is caused by recurrent HSV, but also by primary HSV (rarely)
- Dendritic ulcer (Fig. 7.2)
  - arborescent epithelial ulceration after necrotic vesicles
  - significant corneal hypoesthesia
  - is highlighted by fluorescein staining (ulceration appears green)
  - ulceration may develop in the stroma

    Other causes of dendritic keratitis

    healing of a corneal erosion
    zoster keratitis
    hydrophilic contact lenses
    amoebic keratitis

    Geographic ulcer in which the dendritic branches widen and coalesce to form an ulcer with a geographic, amoeboid configuration

    the use of corticosteroids in dendritic ulcers favors the formation of geographic ulcers

Treatment of epithelial keratitis [11]
- Topical
- Acyclovir 3% ointment (Zovirax) × 5/day
- Ganciclovir 0.15 gel (Virgan) × 5/day
- Trifluorothymidine 1% (Virofta) every 2 h
- mechanical debridement of epithelial branches with a sterile applicator
- general antiviral treatment if necessary

Stromal Keratitis [26, 27]

- **Herpetic disciform keratitis**
  - It is produced by hypersensitivity reaction to viral antigen with stromal inflammation
  - Signs:

    central epithelial edema
    stromal thickening with focal disc and stromal edema without necrosis
    annular stromal infiltrate (Wessely immune ring) around the stromal infiltrate
    Descemet folds
    retrocorneal precipitates

Table 7.4 Clinical forms of herpetic keratitis [2]

Epithelial keratitis 2/3			Stromal keratitis 1/3				
Dendridic	Geographic	Other forms	Interstitial	Disciform	Necrotizing	Kerato-uveitis	Neurotrophic or metaherpetic keratitis
– Aborescent ulcers with reinforced extremities and detached edges	– The area of corneal ulceration extended to surface with irregular edges	– Diffuse KPS – Marginal ulcer	– Localized or diffuse stromal infiltrate – Neovessels	– Healthy epithelium or epithelial keratitis – Stromal edema without necrosis or neovessels – Endothelitis – Immune ring – Precipitates – Corneal hypoesthesia	– Rare – Stromal necrosis with yellowish-white infiltration – Significant inflammation – Risk of descemetocele with perforation	– Stromal keratitis – Hypertensive uveitis – Iris atrophy – Diffuse or localized endothelitis	– Epithelial and stromal damage – Hypoesthesia /corneal anesthesia – Round or oval ulceration – Risk of necrosis, with perforation and super-infection

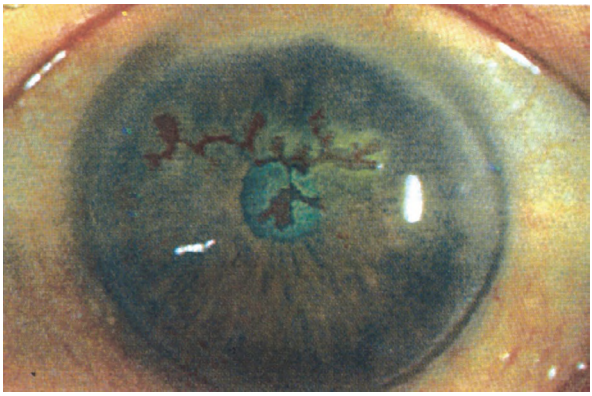

Fig. 7.2 Herpetic-dendritic keratitis

decreased corneal sensitivity
intraocular pressure may be elevated
anterior uveitis in severe forms
sometimes epithelial lesions may be associated

- Treatment:
  - Topical

    steroids × 4/day
    antiviral—Aciclovir
    if there are also epithelial lesions, topical antiviral medication will be administered for 5–7 days, then steroids

- Other causes of central corneal edema
  - acute keratoconus (hydrops)
  - hydrops in keratoglobus
  - Fuchs endothelial dystrophy
  - postoperative edema in cataract

- **Diffuse stromal necrotic keratitis**
  - It is produced by active viral invasion and destruction of the stroma
  - Signs:

    white-caseous necrotic infiltrates
    keratic precipitates
    after several weeks of inflammation, stromal vascularization appears

- Treatment:
  - often without results
  - keratoplasty after treatment of several months with steroids; it can be complicated with recurrence on the new graft

- **Trophic keratitis—metaherpetic**
- The viral disease is not active, but problems similar to the recurrence of a traumatic erosion occur
- Clinically—linear, ovoid, painless epithelial defect.
- Treatment:
  - artificial tears
  - dressing or contact lenses
  - tarsorrhaphy

- **Treatment of herpetic keratitis**

The goals of treatment in herpetic keratitis require: eradication of the virus, suppression of inflammation, promotion of healing, avoidance of recurrences.

Treatment of Superficial Keratitis

- Epithelial debridement that decreases the viral load.
- Antiviral treatment

Locally:
- Virofta (trifluridine) 0.12%—1 drop × 8/day, 7 days, then × 3–4/day, 7 days
- Zovirax (acyclovir) ophthalmic ointment 3% × 5/day, 7 days, then × 3/day, 7 days
- Virgan (ganciclovir) gel—0.15% × 5/day—7 days, then × 3/day, 7 days

Systemically:
- In patients who CANNOT receive local treatment—children, disabled patients
- Zelitrex (valaciclovir) 1 g in 1–2 doses/day
- Zovirax (acyclovir) 2 g/day in 5 doses
  - Adjuvant treatment if the ulcer expands: cycloplegics, antibiotics, analgesics
  - Dressings
  - Eye exam
  - **Pay attention to the epithelial toxicity of antiviral eye drops.**

Treatment of Disciform, Interstitial Keratitis, Acute Keratoveitis.

Ocular
- Corticoids—local
- dexamethasone × 6–8/day until reduction of corneal edema 7–10 days
- laterobulbar injection
- mydriatics, cycloplegics
- cyclosporine eye drops

Systemic
- in severe inflammations
- oral antiviral
  - Zelitrex 2 cp × 3/day until the acute phase is reduced, then 1 cp × 3/day simultaneously with corticosteroid treatment

- duration of treatment up to 3 months, with a slow decrease in doses
- +ocular hypotony treatment

Treatment of Necrotizing Keratitis

- Hospitalization
- Antiviral treatment
- General—per os
  - local
  - virgan (ganciclovir 0.15%, 1 drop × 5/day, 7 days, then 3 drops × 3/day—7 days)

    corticosteroids at subconjunctival onset—dexamethasone 12 h after the onset of antiherpetic treatment

Treatment of Metaherpetic Keratitis

- stopping the toxic treatment with antiviral eye drops
- artificial tears, cicatrizing ointments—autologous serum
- amniotic membrane graft, tarsorrhaphy

Preventive treatment in forms with frequent recurrences is indicated in the presence of three episodes of epithelial keratitis per year or two episodes of stromal keratitis per year by:

- avoiding triggers
- Zelitrex 2–6 tablets/day, 3–5 days after the first signs of relapse
- Corneal graft in keratoveitis

Zoster Keratitis

- It is produced by reactivation of VZV from Gasser's ganglion via the ophthalmic branch of the Vth cranial nerve to the eye and skin; ocular lesions can be caused by direct invasion, secondary inflammation, occlusive vasculitis.
- Clinically:
  - 50% of ophthalmic VZV causes eye damage
  - VZV lesions are strictly limited to the middle of the head
  - Hutchinson's sign—skin blisters in the naso-ciliary nerve territory associated with ocular complications
  - General signs: malaise, fever, pain along the affected nerve, along which blisters appear
- Skin lesions
  - in the distribution area of the nerve; after 3–4 days of flu syndrome with fever, headache, redness and edema appear on the skin of the eyelids followed by blisters, pustules, crusts

  - severe painful neuralgia that subsides after the eruptive phase, but may persist for years; in the territory of the ophthalmic branch of the Vth cranial nerve on the skin of forehead, scalp, upper eyelid, middle 1/3 lower eyelid, wing of the nose and eyeball
  - anesthesia + pain
  - the active phase lasts 3 weeks
- Eye injuries
  - Conjunctivitis—mucopurulent with petechial or follicular hemorrhages with regional adenopathy, rarely necrotizing membranous inflammation.
  - **Zoster keratitis**—may precede neuralgia or skin lesions

    Punctate epithelial keratitis
    microdendritic epithelial ulcer with small stellate pseudodendritic fugitive epithelial lesions
    granular subepithelial nummular keratitis with evolution towards healing or chronicity
    disciform keratitis
    neuroparalytic ulceration
    exposure keratitis if associated VII paralysis
  - episcleritis, scleritis
  - iridocyclitis+ hyphema and hypopyon
  - acute retinal and anterior segment necrosis
  - eye globus atrophy
  - secondary glaucoma
- Complications:
  - neurological

    paralysis of—III—IV—VI—VII cranial nerves
    optic neuritis
    encephalitis
  - ocular

    neurotrophic keratopathy
- Treatment—aims to prevent severe eye damage and postzoster neuralgia.

Local treatment of skin lesions
- antibiotic/corticoid ointment (or lotions)

Local treatment of eye injuries
- zoster keratitis, iridocyclitis, scleritis
- local steroids × 4/day
- cycloplegics
- acyclovir ointment × 5/day, 2 weeks
- prevention of secondary infection—antibiotics

- secondary glaucoma
  - acetazolamide
  - timolol 0.5%
- neuroparalytic ulcer
  - lateral tarsorrhaphy
- persistence of the epithelial defect
  - artificial tears
  - contact lenses, dressing
- Keratoplasty as needed

Systemic

- antivirals: acyclovir 800 mg × 5/day, 10 days or valacyclovir 500 mg, orally, – limit the extension or reduces the severity of keratitis or iritis; they have no effect after the onset of neuralgia
- analgesics—pethidine (in severe forms)
- systemic steroids–inhibit the development of postherpetic neuralgia at high doses, indicated in neurological complications
- cimetidine 300 mg/2–3 weeks reduces pain and pruritus in acute forms
- amitriptyline to combat the depressive component of the disease.

Fungal Keratitis

- It accounts for a small percentage of infectious keratitis in temperate climates, but accounts for 50% of infectious keratitis in tropical climates
- Risk factors for fungal keratitis: vegetative materials trauma, contact lenses carriers, immunosuppression (cancer, leukemia, corticotherapy, chemotherapy), corneo-conjunctival pathology, facial paralysis, corneal surgery [13].

Candida Keratitis

- It is produced in chronic corneal pathology due to the use of corticosteroids over a long period.
- Signs
  - white/yellowish stromal infiltrate resembling bacterial keratitis
  - ulcer with stromal necrosis with possible corneal perforation, severe iridociliary reaction
- Complications: corneal perforation, secondary glaucoma
- Treatment—eye drops with Amphotericin B 0.15% or Fluconazole 0.2%, Voriconazole 1%

***Fusarium* and *Aspergillus keratitis* [23]**

– White/yellowish or gray infiltrate, with feathery edges with linear extensions, surrounded by stromal edema with rapid evolution to necrosis, perforations, endophthalmitis.

Local and general antifungal treatment, associated with antibiotics if necessary

- Locally:
  - amphotericin B 0.15%, Miconazole 1%, Voriconazole 1% (for fusarium), initially 1 drop per hour, 48 h, with progressively reduced rate and continuation of treatment for 3 months
  - subconjunctival—Fluconazole
  - intracameral—Voriconazole 50–100 mg/0.1 cc
- Generally
  - Voriconazole 800 mg/day, Posaconazole 200–400 mg/day
  - risk of perforation—Tetracycline, Doxyclin 100 mg × 2/day
  - antibacterial treatment
  - cyanoacrylate
- Surgical—lamellar or perforating keratoplasty

Amebic Keratitis

- Acanthamoeba is a saprophytic protozoan.
- The occurrence of keratitis is favored by contact lenses wearing, traumatic corneal microulcerations associated with vegetative contamination, rarely opportunistic infections [28].
- Lately, its incidence has increased in contact lenses wearers, the diagnosis is difficult and the treatment unsatisfactory.
- Symptoms: severe eye pain, often disproportionate to clinical signs; lacrimation, photophobia
- Signs:
  - small disseminated, subepithelial or anterior stroma infiltrates, sometimes disciform intrastromal opacities, annular corneal abscess
  - pseudodendritic keratitis may be associated with perineural infltrations (radial keratoneuritis).
- Complications:
  - Corneal thinning, corneal perforation, corneal opacity and neovascularization, iridocyclitis with hypopyon

- Treatment:
  - Oral—Ketoconazole 400 mg/day, Voriconazole 800 mg/day
  - Topical

    propamidine (Brolene 1%), hexamidine (Desomedin), Neomycin, chlorhexidine (0.02 with miconazole), clotrimazole 1%
    duration of treatment 2 weeks—2 months
    cycloplegics
- Surgical: emergency perforating keratoplasty in severe cases.

Deep Parenchymatous, Stromal Keratitis

- Corneal stromal inflammation.

Interstitial Keratitis

Etiologically, interstitial keratitis is:
- bacterial
- syphilis—in the congenital form, it represents 90% of the cause of bilateral vision loss
- TB—unilateral, sectoral
- Leprosy
- Virus
  - HSV, Epstein Bars V, mumps, rubella influenza, measles
- Protozoa—leishmaniasis, malaria, onchocercosis, cysticercosis (*tenia solium*)
- Other causes—sarcoidosis, Hodgkin, Kaposi's sarcoma, mycoses, pigmentary incontinence, Cogan syndrome

Syphilitic Interstitial Keratitis

- 90% congenital syphilis, bilateral, with clinical manifestations at 5–15 years old, unilateral in acquired syphilis;
- signs of congenital syphilis—Hutchinson triad: interstitial keratitis, Hutchinson teeth, otosclerosis
- clinically: interstitial keratitis has a gradual evolution
  - infiltration

    lacrimation, photophobia, pain, blepharospasm

endothelial and stromal edema secondary to anterior uveitis with precipitates, diffuse perikeratic injection;

- florid

  opalescent cornea, through central corneal infiltrate
  radial corneal neovascularization, with "brush-like", "broom-like" vessels penetrating the stroma; the cornea has a fleshy red, cherry appearance with intense subjective phenomena, evolution 2 months

- regression

  progressive reduction of acute inflammation with neovascular invasion with progressive clearing of the cornea from the periphery to the center, evolution 1–2 years; there is obstruction of neoformation vessels that remain filiform cords + leucomatous scars

Treatment:
- Local
- Corticosteroids—Dexamethasone 0.1% 2–3 times
- Atropine
- Keratoplasty if the opacities are dense
- Systemic
  - Penicillin
  - Steroids in refractory forms

Interstitial Keratitis in TB

- Clinically:
  - corneal infiltrates are similar to syphilitic keratitis, but are more frequently unilateral, sectoral
  - it has a longer evolution, with a tendency to relapse
  - inflammatory nodules are smaller, yellowish, but more numerous
- Treatment:
  - systemic—antiTB
  - topical—sterodis and cycloplegics
- **Cogan's syndrome**—ocular inflammation associated with Menière's vestibular dysfunction through an autoimmune mechanism
  - It affects the young adult of 30 years old, with respiratory history (50%), inflammatory vascular diseases 10% (aortic insufficiency, Takayasu disease), polyartheritis nodosa
  - Clinically:

    eye pain, red eye, photophobia

associated with:

conjunctivitis, iritis, episcleritis, scleritis
nausea, vomiting, hearing loss, severe vertigo

- Etiology—syphilis, polyartheritis nodosa, Wegener, sarcoidosis, WKH, sympathetic ophthalmia, cerebellopontine angle tumors
- Treatment—systemic steroids to prevent hearing loss

Peripheral Keratits [16, 29, 30]

Dellen

- It is generated by the instability of the tear film, primary or secondary, of a limbal lesion in relief by the use of rigid contact lenses.
- Clinically—the cornea is thinned peripherally, localized, with intact epithelium
- Treatment:
  - elimination of the cause
  - lubricants

Staphylococcal marginal keratitis

- It is present in chronic staphylococcal blepharitis
- Clinically—marginal subepithelial stromal infiltrate, separated from the limbus by a clear zone (2, 4, 8, 10 o'clock) with neovascularization
- Treatment: topical antibiotics
- Differential diagnosis—bacterial keratitis, c*ontact lens*-associated *corneal infiltrates*, rosacea keratitis.

Rosacea keratitis

- Condition caused by sebaceous gland disease in the skin (10%).
- Clinically:
  - women with facial rash (in butterfly wings) in the malar and nasal area of the face
- At eye level: blepharoconjunctivitis and keratitis with marginal yellowish-white infiltration and small progressive ulcers (sometimes vascularized)
- Treatment:
  - Locally—steroids (frequent recurrence)
  - Systemically—tetracycline 250 mg × 3 weeks, up to 3 months, once daily.

Terrien's marginal degeneration

- Peripheral corneal inflammation (rare) after 40 years, more common in men, bilateral, asymmetric, with slow evolution
- Clinically:

- lesions with supero-nasal onset with punctate opacities in the anterior stroma at the limbus with fine superficial neovascularization
- over time the stroma thins and lesions may expand circumferentially with progressive loss of vision
- spontaneous or posttraumatic perforation is possible
- peripheral, circumferential corneal thinning associated with stromal opacification, superficial vascular pannus, and pseudopterygium
- Treatment:
- correction of astigmatism
- lamellar keratoplasty if needed

Bacterial Marginal Keratitis (Marginal Corneal Ulcer)

- It is produced by infection with *staphylococcus aureus, streptococcus, Pseudomonas* and is associated with blepharitis, conjunctivitis.
- Symptoms—nonspecific with acute onset: moderate eye pain, foreign body sensation, red eye.
- Clinically:
  - stromal infiltrate at the periphery of the cornea parallel to the limbus with circumferential extension
  - erosion at the level of the infiltrate with marginal corneal ulceration, neovessels
  - signs of blepharoconjunctivitis
- Treatment:
  - local

    antibiotics according to antibiogram
    topical corticosteroids

  - systemic—tetracycline, doxycycline

Marginal Keratitis in Contact Lens Wearers

- Clinically:
  - localized conjunctival hyperemia
  - round or oval peripheral corneal infiltrate under 1.5 mm, white/yellow, with epithelial defect that can be superinfected
- Treatment:
  - spontaneous regression using intermittent contact lenses
  - monitoring of bacterial superinfection

Mooren's Ulcer

It is a peripheral idiopathic corneal ulceration, painful, progressive, with circumferential evolution in clinical forms: benign (unilateral, 25%, limited), malignant (bilateral, 75%, painful).

- Symptoms: pain, photophobia, decreased visual acuity
- Clinically:
  - peripheral corneal stromal infiltrate 2–3 mm from the nasal or temporal limbus with peripheral corneal ulceration with central and circumferential evolution, with neovascularization, possible perforation in severe cases
  - possible iris, episcleral inflammation
- Clinical forms:
  - benign—unilateral, slow progression
  - progressive—virulent, bilateral in young people with rapidly progressive ulcer, with scleral involvement
  - slightly prominent peripheral corneal ulceration extending into surface and depth, with corneal thinning (+ perforation), vascularization and corneal fibrosis
- Differential diagnosis
  - Terrien's marginal degeneration with painless, noninflammatory corneal ulceration with peripheral corneal thinning without ulceration
  - Pellucid marginal degeneration with inferiorly thinned cornea with irregular astigmatism
- Treatment—young people respond favorably to corticosteroids, elderly people require immunosuppressants.
  - Topic

    Antibiotics—Moxifloxacin to prevent bacterial superinfection
    Immunosuppressants—ciclosporin, methotrexate, mycophenolate mofetil, azathioprine
    Interferon 2b
    Cycloplegics
    Therapeutic contact lenses
    Artificial tears

  - Systemic

    Prednisolone 60–100 mg tapering
    Immunosuppressants—cyclophosphamide, azathioprine, methotrexate
    Interferon with antiviral medication—Ribavirin

- Surgical treatment in refractory cases
  - Surgical excision, keratoepithelioplasty, corneal keratectomy, keratoplasty, cryotherapy + surgical excision

Immune Mediated Keratitis [6, 18]

Corneal Diseases Associated with Rheumatoid Arthritis (RA)

RA is a chronic inflammation of unknown etiology that initially affects the joint synovium and frequently the eye.

At ocular level:
- decreased vision, foreign body sensation, pain, conjunctival inflammation with chemosis, exudative retinal detachment
- may be associated with keratoconjunctivitis sicca (most common), ulcerative keratitis, diffuse episcleritis, marginal corneal infiltrate and marginal corneal thinning.
- Treatment
  - systemic therapy with: NSAIDs, corticosteroids, immunosuppressants: methotrexate, sulfasalazine, ciclosporin, gold, etanercept (Enfrel)
  - locally

    keratoconjunctivitis sicca treatment
    ciclosporin A

  - surgery is sometimes necessary—perforating keratoplasty

Corneal Diseases Associated with Other Collagen Diseases

- They are chronic ocular inflammations present in systemic diseases with damage to the supporting tissue, polymyositis and dermatomyositis and vasculitis in Wegener's granulomatosis, polyarteritis nodosa, Behcet's disease
- Ocularly: keratoconjunctivitis sicca, episcleritis, scleritis, associated keratitis
- Treatment—of the systemic condition with immunomodulators and immunosuppressants

Wegener's granulomatosis, periarteritis nodosa, SLE
- Peripheral corneal ulceration that may extend to the sclera
- Painless ulceration, difficult to treat
- Treatment
  - Topical: corticosteroids and cyclosporine
  - Systemic: corticosteroids and immunosuppressants
  - Corneal graft on the verge of perforation

Non-Infectious Keratites

- There are corneal disorders produced by various causes:
  - inflammations: blepharitis, conjunctivitis
  - injuries: foreign bodies, contact lenses, exposure keratitis
  - age-related: ectropion with trichiasis, spastic entropion, keratoconjunctivitis sicca
  - cataract operations, glaucoma
- **Superficial punctate keratitis** (Table 7.5)
- Multiple lesions in the superficial layer of the cornea, epithelium, Bowman's membrane by:
  - viral infections: HZV, adeno-pharyngoconjunctival infection, HSV
  - *Chlamydia*—trachoma, inclusion conjunctivitis
  - exposure and neuroparalytic keratitis
  - allergies—vernal kerato-conjunctivitis
  - irritations—IDU
  - dry eye
  - photoophthalmia
  - specific, idiopathic, Thygeson, superior limbic kerato-conjunctivitis.
- Clinically
  - fluorescein-stained, superficial, punctate epithelial lesions accompanied by pain, lacrimation, photophobia, frequently associated with conjunctivitis, blepharospasm, variable decrease in visual acuity
  - various morphological types—multiple superficial erosions, epithelial, subepithelial punctate lesions, filamentary keratitis
- To follow: history, upper and lower conjunctival sac fundus after eyelid inversion, blink quality, corneal sensitivity, tear film (Schirmer test)
- Treatment:
  - Local

    Artificial tears
    Corticoids
  - specific to the case
- **Exposure keratitis—lagophthalmos**
- **Neuroparalytic keratitis**
- **Keratitis through contact lenses**
  - Corneal lesions with sometimes severe symptoms and signs of inflammation up to corneal ulceration and peripheral corneal vasculature through rigid contact lenses
  - Symptoms:

Table 7.5 SPK according to localization

	Marginal	Sectorial localization	Central	Diffuse	1/3 upper	1/3 lower
Causes	– Contact lenses – Pterygium – Pinguecula – Limbus, cornea tumors	– Subpalpebral foreign body – Trichiasis – HSV, VZV	– KC sicca – HSV, adeno-pharyngoconjunctival – Contact lenses – U.V. – Lagophthalmos – Thygeson's keratitis	– Allergic KC – Severe corneal dryness – Acute conjunctivitis – Trachoma	– Vernal KC – Trachoma – Limbic corenal keratitis – Limbic keratoconjunctivitis – Contact lenses – Blepharitis	– Keratoconjunctivis sicca in: – Collagenoses (Sjögren, RP, SLE, Wegener) – Infiltrations in sarcoidosis, fibrosis (postradical) of the lacrimal gland – Conjunctival scars in trachoma, chemical burns, Stevens Johnson, Lyell – Medicines: contraceptives, antihistamines, beta blockers, atropine – Blepharitis – Palpebral malposition: ectropion, lagophthalmia, VII palsy, entropion
Clinic		– Recurrent keratitis – History of trauma, Cogan's dystrophy	– Punctate lesions in the epithelium, Bowman's membrane, fluorescein staining+	– Corneal edema in: cornea guttata, Fuchs dystrophy, pseudophakic, aphakic	– Similar SPK with central	– Chronic, bilateral dry eye syndrome, lacrimation, red eye

Eye discomfort
Cessation of sight

– Signs:

Contact lenses can mask the epithelial corneal defect (highlighted by fluorescein)
Giant-papillary superior limbic keratoconjunctivitis and protrusion of connective tissue in the upper tarsus.

– Treatment:

Discontinuous wear of contact lenses, use of other types of contact lens
Topical—steroids with corneal monitoring

- **Bullous keratopathy**
- Corneal epithelial blisters and corneal opacification by decreased endothelial cell function.
- Bullous keratopathy is the most common indication for corneal transplantation.
- Functional impairment of the corneal endothelium is caused by: inflammation, trauma, surgical interventions of the anterior pole (cataract, glaucoma) with corneal hydration disorders, with corneal edema and epithelial bubbles; the decrease in endothelial cells may also be genetic in Fuchs' endothelial dystrophy.
- Symptoms:

progressive visual acuity decrease, initially in the morning upon waking (the cornea hydrates at night by closing the eyes).

- Signs:

thinning of the cornea
epithelial edema
epithelial bubbles

- Treatment:

5% hyperosmolar solutions
perforating corneal transplantation

- **Thygeson's superficial punctate keratitis**

– Bilateral superficial punctate keratitis, chronic, of viral or allergic origin, with spontaneous remissions and intermittent exacerbations
– Symptoms:

lacrimation, photophobia
asymptomatic
foreign body sensation

– Signs: epithelial punctate keratitis, circular, oval or stellate, in the center of the cornea, stained with fluorescein in the acute phase.
– Treatment:

self-limited with remissions; it disappears after 5–6 years
in the acute phases—local steroids, with rapid resolution of the lesions, after 1–2 months, but possible relapses after 6–8 weeks
Therapeutic contact lenses
Trifluridine (viroptic)
Topical cyclosporine

- **Filamentary keratitis**
  - It is a superficial punctate keratitis associated with the formation of epithelial corneal filaments by:

    keratoconjunctivitis sicca
    recurrent erosion
    bullous keratopathy
    neurotrophic keratitis
    neuroparalytic keratitis
    radiation keratitis
    HSV keratitis, adenovirus
    Thygeson's keratitis, trachoma
    prolonged dressing after cataract surgery
    systemic diseases: diabetes, psoriasis
    idiopathic
    toxic local medication

  - Symptoms:

    moderate pain
    eye irritation
    lacrimation
    foreign body sensation

  - Signs:

    elongated filaments in the epithelium, attached at the base, with mucus and free degenerate cells above the cornea
    superficial punctate keratitis

  - Treatment:

    mechanical debridement of filaments and 24-h dressing with lubricating drops
    therapeutic contact lenses
    causal treatment
    acetylcysteine

Neurokeratopathies [31]

Exposure Keratitis (lagophthalmic)

- Clinically:
  - insufficient closure of the eyelids provides conditions for exposure keratitis and is determined by: VIIth nerve palsy, extreme exophthalmos, severe ectropion, coma.
  - epithelial punctate keratitis, which favors necrosis, ulceration, bacterial superinfection, perforation, neovascularization through corneal dryness in the interpalpebral space
  - initially inferior epithelial keratitis
  - evolving towards inferior corneal ulceration
- Treatment
  - Prophylactic

    artificial tears
    ointments
    dressing, contact lenses
    causal treatment

  - Curative treatment
  - Treatment of corneal ulcer

    eye lubricants (often artificial tears)
    ointment with cicatrizing agents
    nocturnal eyelid occlusion
    tarsorrhaphy

Neuroparalytic Keratitis

Congenital
- Causes:
- Congenital
- anhidrotic ectodermal dysplasia
- familial dysautonomia (Riley-Day)
- congenital insensitivity to pain
- acoustic neuroma
- abuse of local anesthetics
- Acquired:
- by paralysis of the ophthalmic branch of the Vth cranial nerve (without corneal sensitivity) by: *alcoholization* of the *Gasserian ganglion*
- compressive neoplasm on Gasser's ganglion

- VZV, HSV
- neuropathy related to syphilis, leprosy
- diabetes
- Clinically:
  - Painless, decreased corneal sensitivity
  - Initially punctate keratitis with epithelial erosions in the interpalpebral space, followed by central stromal ulceration (by exfoliation of the corneal epithelium), with evolution towards perforation
  - discrepancy between the absence of symptoms and the severity of the progression of corneal ulceration to perforation
- Treatment:
  - Local

    atropine
    antibiotic
    artificial tears
  - Surgical

    lateral tarsorrhaphy if needed
    amniotic membrane transplantation

Recurrent Corneal Erosion Syndrome (Fig. 7.3)

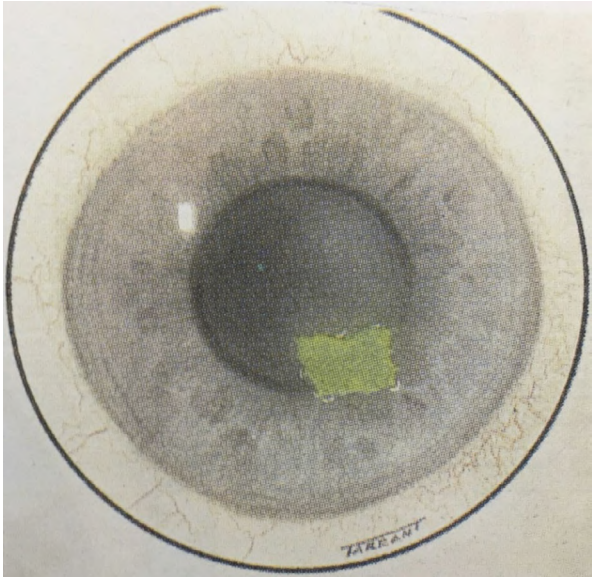

Fig. 7.3 Corneal erosion

- Defect of adhesion of the corneal epithelium to the basement membrane with spontaneous rupture of the corneal epithelium occurring in the morning on awakening after previous corneal erosion in which adequate adhesions have not been formed between the healed epithelium and the basement membrane or without a history of trauma if it is a dystrophy of the basement membrane.
- Causes:
  - superficial corneal trauma
  - Cogan corneal dystrophy
- Symptoms:
  - brutal pain
  - lacrimation
  - photophobia
  - visual acuity lowering in the morning
- Signs:
  - corneal microerosions associated with basal lamina dystrophy
  - macroerosion surrounded by elevated perilesional epithelium, often with a history of trauma
- Treatment → of the erosion
  - Local:

    artificial tears
    cycloplegics
    hyperosmotic NaCl 2.5–5% for 2 months
    NSAID eye drops
    debridement in severe forms
    contact lenses, eye dressing—6 months

  - Preventive:

    Artificial tears
    Extended wear contact lenses
    Excimer laser phototherapeutic keratectomy
    oral tetracycline
    micropunctures of the anterior stroma in peripheral erosion after trauma

Drug-Induced Keratopathy

Chrysiasis

- Gold deposits in the healthy cornea after prolonged administration of gold salts in the treatment of rheumatoid arthritis.

- Clinically:
  - asymptomatic bright stromal opacities
  - peripheral subepithelial infiltrates and stromal neovascularization (rarely)

Cornea verticillata

- It is present in the treatment with antimalarial drugs (chloroquine, hydroxychloroquine) where it is irreversible and amiodarone, reversible depending on the dose.
- It can cause crystalline deposits and optic neuropathy.
- Clinically: clustered filamentary corneal opacities initially located centrally that extend laterally.

Metabolic Keratopathy

Cystinosis

- Hereditary AR (17p gene) disorder by lysosomal transport abnormality with diffuse cysteine crystal deposition.
- Signs:
  - progressive deposits of cysteine crystals causing eye discomfort and decreased visual acuity.
  - treatment: cysteamine eye drops 2%

Deposits of Immunoglobins

- Etiology—leukemia, multiple myeloma, Waldenström macroglobulinemia, lymphoproliferative syndromes.
- Signs: flake-like bilateral posterior stromal opacities
- Treatment—corticosteroids or chemotherapy for underlying pathology

Mucopolysaccharidosis (MPS)

- Hereditary disease AR (except for Hunter disease which is sex-linked RA), by deficiency of glycosidase required for the hydrolysis of muco-polysaccharides.

- Clinically—corneal opacification in all MPSs except for Hunter and Sanfilipo syndromes

Wilson's Disease: Hepatolenticular Degeneration

- Metabolic abnormality due to ceruloplasmin deficiency responsible for cellular copper deposits.
- Signs:
  - Kayser-Fleischer ring, copper deposits in the peripheral portion of Descemet's membrane
  - anterior capsular cataract-turnesol flower-shaped.

Emergencies in Corneal Pathology

Corneal Abrasion

- Corneal microtraumas (finger strike, tree branches, foreign body, contact lenses)
- Clinically:
  - foreign body sensation
  - lacrimation
  - photophobia
  - sharp pain (in contrast to the pain of iritis and some conjunctivitis where the pain is under the form of an intermittent discomfort)
  - the highlighting by fluorescein staining of corneal deepithelialization
- treatment
  - etiological (extraction of the foreign body from the surface of the eyelid, cornea, conjunctiva if any)
  - topical:
- antibiotic (eye drops, ointment)
- cycloplegic to reduce ciliary spasm
- eye dressing
- *NO STEROIDS*
- systemic—analgesics as needed
- **pay attention to corneal abrasions due to contact lenses where there is a risk of infectious keratitis (with *Acanthamoeba*)**

Corneal Foreign Body

- Clinically:
  - foreign body sensation
  - lacrimation, photophobia
  - decrease in visual acuity after localization, age
  - red + painful eye
- Treatment:
  - topical anesthetic (allows examination)
  - foreign body removal by:

    corneal irrigation
    biomicroscope extraction of the foreign body, with a spatulated needle (carefully because the cornea is thin)—0.5 mm centrally, 0.7 mm peripherally
  - removing the rust area (if the metal foreign body was old)
  - post-extraction

    topical:

    antibiotic (ointment)
    cycloplegics
    dressing 24 h
    check-up after 24 h, continuation or not of treatment depending on the clinical aspect

Corneal Burns

Corneal burns according to the etiological agent can be: thermal burns and chemical burns with acids, bases.

Thermal Burns

They are injuries of the ocular surface that predominantly affect the corneal epithelium with the limitation of the extension of the lesions in the deeper layers by closing the palpebral fissure caused by the rapid blink reflex and the Bell phenomenon.

Thermal burn can be caused by contact with gases, hot liquids, molten metal, electric flame burn.

Symptoms—of a corneal erosion with: photophobia, lacrimation, foreign body sensation.

Clinically:
- corneal de-epithelialization limited to the epithelium in most cases, through its coagulation
- in severe forms, the deep layers of the cornea are affected with an opaque porcelain cornea
- myositis
- ciliary reaction in severe forms

Treatment:
- removal of foreign bodies (if any)
- topical antibiotics to avoid superinfection
- local:
  - NSAIDs
  - cycloplegics
  - therapeutic contact lenses
  - dressing, healing ointments
  - limited debridement of devitalized tissues (if any)
- **Patients exposed to UV light** may have damage to the corneal epithelium (exposure to the sun, snow, electric flame)
- Clinically: 6–12 h after exposure:
  - photophobia, foreign body sensation, pain, lacrimation, blepharospasm
  - red eye with bilateral punctate keratitis
  - palpebral conjunctival edema
- Treatment:
  - warm compresses
  - oral analgesics
  - topical:

    antibiotics
    eye dressing

Chemical Burns

Chemical burns of the eye are serious and represent major emergencies, their severity being dependent on the nature of the chemical agent, duration of contact, exposed surface area, concentration and penetration power

- corneal chemical burns may also involve other structures of the anterior segment (iris, ciliary body) with severe consequences on vision with decreased, loss of vision.

Etiologically, the burns are with:
- acids
- sulfuric (most common) acetic, chromic
- acid burns cause the denaturation and precipitation of proteins, self-limiting the penetration of the causative factor of the burn in depth → it is the **coagulation burn** of the cornea (the cornea having a frosted glass appearance)
- bases (ammonia, soda, potassium hydroxide, lime)
  - bases dissociate at the ocular surface and penetrate the corneal layers with the destruction of stromal collagen, release of prostaglandins, increased intraocular pressure and iridociliary reaction
  - base burns have a prolonged caustic action and cause necrosis of the corneal epithelium and stroma, with neovascularization
  - base burns produce **liquefactive necrosis**

Medical Treatment: Immediate Emergency

– Abundant washes of the anterior ocular surface

Burns (stage 1,2)
- Local
- topical antibiotics—Ofloxacin, Moxifloxacin
- cycloplegics (NOT phenylephrine which accentuates perilimbal ischemia)

Severe burns
- Local treatment
- N acetylcysteine eye drops
- healing ointment
- contact lenses
- dressing
- prevention of symblepharon by debridement
- Systemic treatment
  - Doxycycline 100 mg × 2/day
  - ocular hypotonics
  - control of inflammation by corticosteroids: NSAIDs
  - vitamin C in alcohol burns (decrease the incidence of corneal ulceration)
- Early surgical treatment
  - advancement of Tenon's capsule and suture to the limbus
  - tissue adhesives to prevent corneal perforation
  - amniotic membrane graft
  - stem cell transplantation
  - late

    release of cicatricial clamps

treatment of symblepharon and palpebral deformities
lamellar keratoplasty after 6 months
keratoprosthesis

Traumatic Hyphema

Represents the presence of blood in the anterior chamber secondary to ocular trauma by: contusions: 70% by trauma to the ciliary body or penetrating wound

- Clinically:
  - hyphema sizes are variable: small, medium, total
  - partial or total resorption in a few days, sometimes with rebleeding
  - slow resorption of hyphema is accompanied by hematic impregnation of the cornea.
  - Complications—immediate or late secondary glaucoma
- Treatment
  - medical:

    cycloplegics
    topical corticosteroids
    epsilon aminocaproic acid

  - surgical

    intracameral plasminogen activator for clot lysis
    anterior chamber wash

Corneal Abscess

Serious eye disease caused by: bacteria, fungi, amoebae.

- Contributing factors:
  - young: contact lenses carriers, posttraumatic (foreign body), burns
  - elderly patients: dry eye, palpebral deviations, chronic corneal diseases (bullous dystrophy, corneal ulcer, trachoma)
  - at all ages: postsurgical (refractive surgery, cornea graft) in immunosuppressed patients (diabetes, corticotherapy), alcoholics, malnourished
- Symptoms:
  - pains with rapid onset, variable intensity
  - decrease in visual acuity

  - photophobia, lacrimation, blepharospasm
  - eyelid edema

- Clinically:

  - epithelial ulcer with localized (abscess) or diffuse corneal infiltrate
  - perikeratic hyperemia
  - Tyndall of the anterior chamber or hypopyon.

The clinical appearance is variable depending on the etiological factors.

- **Gram (+) cocci** represent 80–90% of the causes of corneal abscess—staphylococcus, streptococcus

  - Round or oval, grayish, white, with sharp edges abscess, hypopyon and rapid evolution

- **Gram (−) bacilli** represent 10–20% of the causes of corneal abscess: pseudomonas, Enterobacter

  - diffuse abscess, with rapid evolution towards necrosis with significant perilesional edema, hypopyon
  - mucopurulent discharge

- **Gram (−) cocci** *Neisseria Gonoreea* with rapid evolution
- **Fungi** generate keratomycosis in: vegetative materials trauma, prolonged use of corticosteroids for chronic diseases

  - Slightly painful corneal abscess with gray surface, with satellite microabscesses and hypopyon

- **Amoeba**

  - in contact lenses carriers with poor hygiene, inadequate maintenance of contact lenses (tap water, swimming pool), trauma
  - eye pain disproportionate to corneal involvement (often patients are treated for herpetic keratitis)
  - subepithelial infiltrate, radial keratoneuritis (pathagnomonic but rare)
  - after 1–2 months of evolution—deep corneal involvement with disciform stromal infiltrate, ring, immunitary, intense eye pain, ocular hypertonia, scleritis

- Severity criteria for corneal abscess

  - Locally:

    the diameter of the abscess, the position of the abscess, the severity of the iridociliary reaction
    bilateral damage

virulence of the germ
the imminence of perforation
associated diseases: endophthalmitis, scleritis

- Treatment of the corneal abscess
  - Contact lenses carriers: ciprofloxacin 1 drop/hour, gentamicin, desomedine 0.1% if is *Acanthamoeba* keratitis
  - In non-wearers—ofloxacin (Exocrin) 1 drop per hour, Rifampicin
  - Posttraumatic: ciprofloxacin (Ciloxan), Bacitracin, amphotericin B 2 mg/ml in keratomycosis
  - Antibiotics are initially administered every 5–10 min, after 48 h/per hour for 15 days
- Performing an antibiogram culture
- Bacterial keratitis where sight is threatened, reinforced eye drops—gentamicin 15 mg/ml, vancomycin 50 mg/ml are used
- Keratomycosis:
  - Local amphotericin B and fluconazole 2%
  - Generally:

    Fluconazole (Triflucan)
    Voriconazole
- Endophthalmitis or adverse outcome
  - Locally:

    Intravitreal + intracameral amphotericin B (single or combined—maximum dose 10 μg)
    Voriconazole eye drops 1% (filamentary)
  - Systemic—azoles: (hepatic balance), fluconazole, voriconazole, caspofungin
- Amebic keratitis
  - Locally:

    Hexamedin (Desomedin)
    Colmycin (reinforced 125,000 U/ml)
    PHMB 0.02% eye drops
    Vismed (as needed), 1 drop per hour for 3 days, then at 2.4 h, × 5/day, 1–3 weeks, × 3–4/day, 2–4 months
    Corticotherapy according to the clinical aspect
  - -Generally—in systemic stromal involvement, associated scleritis

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Chapter 8
Contact Lenses

Cristina Nicula and Ariadna Patricia Nicula

Abstract Contact lenses (CL) are commonly used to correct refractive troubles, aphakia, keratoconus, irregular cornea, anisometropia, in the management of dry eye, after corneal or crystalline refractive surgery, in relapsing epithelial erosion syndrome, for therapeutical reasons and for cosmetic purposes (common). Although the CL wear offers a number of advantages, their inappropriate use can generate complications that sometimes require stopping wearing them. Generally, CL are divided into two main groups, depending on the type of material rigid CL and soft CL, each with its advantages and disadvantages.

Contact lens complications are represented by discomfort related to contact lens wear, corneal neovascularisation, keratitis related to CL wear (peripheral keratitis, microbial keratitis, keratitis with Acanthamoeba, fungal keratitis), giganto-papillary conjunctivitis, arcuate superior epithelial lesion, corneal edema, deposits, contact lens damage.Therapeutical contact lenses are indicated for pain relievers, healing purposes, hydration purposes, for protective reasons, rehabilitation after eye surgery, for support purposes and for delivering drugs. Orthokeratology is an alternative method of temporary correction of refractive errors by modifying the curvature of the cornea. Modern orthokeratology uses lenses made of rigid materials with reverse geometry for a better modification of the corneal shape. Myopia is the most frequent indication of orthokeratology lenses. By providing good vision without correction during the day, it has become a particularly popular corrective alternative among children.

Keywords Contact lenses · Complications · Types · Orthokeratology

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- Contact lenses (CL) are commonly used:
  - to correct refractive troubles;
  - in the correction of aphakia, keratoconus, irregular cornea and large anisometropia, alternative to wearing glasses;
  - in the dry eye management from Steven-Johnson syndrome or Sjogren's syndrome;
  - after corneal or crystalline refractive surgery;
  - in relapsing epithelial erosion syndrome;
  - for cosmetic purposes (common).
- The use of CL has considerably improved patients' quality of life, providing an excellent aesthetic appearance without restricting daily activity [1]. Although the CL port offers a number of advantages, their inappropriate use can generate complications that sometimes require stopping wearing them [2].
- CL indications depend on the purpose for which they are recommended.

Indications for Optical Purposes

- hyperopia of any degree;
- myopia of varying degrees, especially in high myopia where CL correction may provide better visual acuity than correction with glasses;
- regular or irregular astigmatism (keratoconus, corneal ectasias, after corneal graft)
- presbyopia;
- unilateral aphakia;
- anisometropes [3].

Therapeutic Indications

- bullous keratopathy associated with chronic corneal edema generated by endothelial decompensation;
- relapsing corneal erosion syndrome generated by previous causes (corneal trauma, epithelial or stromal distrophies) [3];
- persistent epithelial defects and corneal ulcers, including ulcers of infectious, trophic or autoimmune etiology;
- corneal irregularities;
- superficial Thygeson punctate and superior limbic keratitis;
- filamentous keratitis;
- small corneal perforations (corneal wounds, perforated ulcers);
- rehabilitation after eye surgery (keratoplasty, photokeratectomy, keratomileusis *in situ*, corneal *cross-linking* therapy).

Contact Lens Indications for Aesthetic/Cosmetic Purposes

Aesthetic indications—recommended for those in whom glasses constitute an aesthetic disability or want to become independent of glasses. They can be indicated to those who want to change the iris color.

Cosmetic indications—in patients who have suffered an eye injury and present an unsightly eyeball, or aniridia, polychoria or coloboma of the iris [3].

Contraindications of Contact Lenses

- lack of motivation related to the CL wear;
- manual problems: in the elderly, those with Parkinson's disease, in those with paralysis;
- neurotic patient, mental illness;
- polluted working environment (smoke, dust, sawdust);
- corneal disorders: corneal anesthesia and hypoesthesia, corneal ulceration, Sicca syndrome (relative contraindication);
- acute or chronic inflammation of the cornea;
- disorders of the conjunctiva : acute or chronic inflammation, pinguecula, large pterygium with extension on the cornea;
- diseases of the eyelids or lacrimal apparatus: acute or chronic inflammation;
- medical conditions: epilepsy;
- lack of local hygiene or regular check-ups [1, 2];
- general conditions: diabetes mellitus, use of oral contraceptives, pregnancy, confinement, bronchial asthma, contact dermatitis, allergic rhinitis.

Advantages

- provides a full field of vision and added safety, as the wearer can see with CL on the eye at any angle;
- allow the wearing of sunglasses or protective glasses;
- provides aesthetic comfort;
- visible makeup, easier to apply and wear;
- they do not fog up and do not limit the field of vision, even if it rains or snows outside;
- allow the practice of various activities.

Disadvantages

- application of CL can create problems at first. Until the manual of putting on and removing the lens is gained, they can be damaged or even lost.
- CL do not protect the eyes from blue light. Patients who work a lot at the computer or spend a lot of time in front of the TV and mobile devices, wearing only CL, risk later developing eye fatigue syndrome, caused by blue light. In this case, the only protection solution is glasses with protection for blue light**.**
- requires increased attention and proper hygiene. CLs are devices that are applied directly to the eyes, as such their handling must be done carefully and in a clean environment. Hands should be thoroughly washed and dried before applying or removing lenses, which is not always possible. In many of these situations, disposable CL are opted for.
- worn improperly, they can cause redness, irritation and dryness. If the patient accidentally falls asleep with daily CL, wears them longer than their shelf life or does not care for them properly, there is a risk of developing CL-induced complications, from mild to most severe.
- they are more expensive than glasses. In addition, it is also necessary to purchase complementary products (maintenance solution, lens storage containers, artificial tears).

Types of Contact Lenses

Generally, CL are divided into two main groups**, depending on the type of material: rigid CL and soft CL**, each with its advantages and disadvantages.

The types of lenses are: rigid, soft, disposable lenses, daily lenses (bi-annual, monthly, etc.), extended wear lenses, continuous wearing lenses, bifocal or multifocal lenses.

Rigid Contact Lenses

- Advantages:
  - are more durable and resistant to protein deposits than soft lenses;
  - allow oxygen to go through the lens to the cornea and keep their shape intact;
  - provides clearer vision in case of astigmatism problems (cylindrical diopter);
  - they are also a good long-term investment, as they can be worn from several months to 2 years (annual contact lenses).

- Disadvantages
  - The biggest disadvantage of rigid lenses is discomfort when wearing. Accommodation can take up to several weeks.
  - If they are not worn for a few days, the eye will take a while to readjust.
  - They are smaller in size than soft lenses, so the risk of moving away from the center of the eye is higher, and wearers may have blurred vision.
  - It moves on the eye when blinking, the risk of dust getting under the lens is higher. Due to dust, corneal erosions may occur.

Soft Contact Lenses

- Advantages
  - They are produced of a soft and flexible plastic that allows oxygen to penetrate to the cornea, thus maintaining eye health.
  - The adaptation of the eye to these lenses is much easier and faster (a few days).
  - It is the most accepted type of lens, which is also keep up by market figures: soft CL are the first in the top, used by 92% of wearers.
- Disadvantages
  - They are more sensitive to protein deposits and require increased attention in lens care.
  - The shelf life is shorter than that of rigid lenses—maximum 30 days. This is not necessarily a disadvantage, but as an investment this type of lenses can be more expensive on long term.

Soft Hydrogel Contact Lenses

- Advantages
  - Hydrogel is a material that transports oxygen to the eyes with the help of water in the composition. Having a high water composition, hydrogel lenses are especially recommended for patients who have dry eye syndrome and who cannot support any other material (silicone-hydrogel).
- Disadvantages
  - mode of wearing. Hydrogel lenses cannot be worn for more than 8 h a day because the amount of water in the lens decreases, and after the recommended 8 h, the lens becomes uncomfortable.

Silicone-Hydrogel Soft Contact Lenses

- Advantages
  - silicone hydrogel is a upper-level material to hydrogel, and oxygen transmissibility (Dk/t) can be as high as ten times. These lenses can be shabby continuously for a period of 30 days, after which the lens must be changed.
  - the initial water level is lower compared to Hydrogel lenses, minimizing the risk of bacterial growth.
- Disadvantages
  - Having a lower water level, these lenses are not very suitable for people who have dry eye syndrome, even though some have a water level of almost 50%.

Contact Lens Complications

Discomfort Related to Contact Lens Wear

- According to the Society of Tear Film and Ocular Surface (TFOS), CL wear related discomfort (DLC) is described as a situation characterized by transient or constant eye sensations related to the CL wear, accompanying or not with vision impairment, causing reduced compatibility between CL and the environment. This complication will generate reduced port time of the CL or even discontinuity or abandonment of the CL wear.
  The prevalence of DLC occurs between 23% and 94% of patients with symptoms related to the CL wear.
- The factors that cause DLC may be related to CL or environmental factors. Factors related to CL are material (water content), CL design (edge, asphericity), adaptation, wear program and cleaning system (chemical composition of the solution)
- Environmental factors may be related to the ocular surface (dry eye syndrome, tear film composition), environmental factors (humidity, currents, temperature), job related habits (computer, blinking less often, light), medication, compliance, other factors (age, gender, ocular history or general illness, mental illness).
- Symptoms appear after the initial adaptation period and disappear upon removal of the CL. Sometimes they can be accompanied by hyperemia of the conjunctiva or sometimes they can be diagnosed only on the basis of the symptoms declared by the patient [3, 4].

  Management to provide daily comfort at the CL wear, necessary for carrying out the patient's daily activities.

- The evaluation of the factors that generate DLC will be done at the patient's first visit, on the occasion of CL adaptation. In this regard**, a rigorous anamnesis, slit lamp examination and tear film testing** are necessary to estimate risk factors for DLC (blepharitis, meibomite, dry eye syndrome) before CL port.
- **DLC can be prevented** in patients at high risk of developing the complication through daily CL use, disposable CL use, use of hydrogen peroxide CL cleaning systems (more compliant), and topical use of artificial tears.
- For symptomatic patients, the **anamnesis should highlight the causes of the complication,** namely how long after CL application symptoms appear, how many times they manifest during the day, CL type, what cleaning system the patient uses, whether there are associated eye or systemic diseases (allergy), use of ocular or systemic medication or environmental factors. Other **ocular or systemic diseases** unrelated to the CL wear **should be also treated**. Diseases of the conjunctiva such as internal pterygium, pinguecula or chemosis of the conjunctiva can cause eye discomfort and can be aggravated by the CL wear. Additionally, corneal diseases (corneal dystrophies, relapsing corneal erosion syndrome) can cause symptoms that can mimic DLC. Slit lamp examination can show these pathologies. If the patient with these pathologies wants to wear CL, they need to be treated medically or surgically, before adjusting the CL.
- **Control of environmental conditions:** increasing humidity, avoiding air conditioning, looking away for a few minutes while working at the computer [5, 6].
- One of the key causes of DLC is the patient's **lack of compliance** with the pace of change of CL, the use of cleaning systems and artificial tears [7]. Effective treatments have been proposed to reduce dry eye phenomena.

Corneal Neovascularisation

- Corneal neovascularization is an invasion of the cornea with vessels originating from the perilimbal plexus, which advance to the stroma.
- The complication occurs in 1–20% of CL carriers [8]. Patients using rigid gas permeable CL (RGP) or polymethylmethacrylate (PMMA) have a lower complication rate [9]. The incidence is higher in soft CLs and especially in those with extended wear [9].
- As risk factors involved in the occurrence of complication are: CL material characteristics (oxygen transmissibility), refraction error (influences the thickness of the CL periphery in the hydrogel, decreasing transmissibility to the CL periphery) or improper adaptation of CL [10, 11].
- In addition, deep herpetic keratitis and corneal graft may result in corneal neovascularization [12].

Management

– It is recommended to substitute the CL with a CL with an improved oxygen permeability, change the port rate from extended to daily, switch to LCRGP from CL silicone hydrogel and discontinuity or even abandonment of the CL port in cases with active and progressive neovascularization [13, 14].
– In these cases, injections of subconjunctival antivascular endothelial growth factor (antiVEGF) agents are recommended in combination with steroid or nonsteroidal anti-inflammatory drugs [15, 16]. In severe cases, stem cell transplantation is indicated [17, 18].

Keratitis Related to CL Port

Peripheral Keratitis Related to CL Port

– CL port-bound peripheral keratitis (CLPU) is characterized by an epithelium depression accompanied by infiltrate and an intact Bowman membrane.
– This complication occurs in the presence of Staphylococcus aureus and corneal erosion. Immunological agents and bacterial toxins that enter the cornea through erosion can cause inflammation and corneal infiltration [19, 20].

CLPU is more common in prolonged port (26%) and in silicone-hydrogel CL carriers 92–93% [21].

CLPU is characterized by mild, localized conjunctival congestion and the presence of a focal infiltrate, smaller than 1.5 mm, grey, placed in the corneal periphery.

Management

– It is recommended to replace the CL with one with improved oxygen permeability, change the port rate from extended to daily, switch to LCRGP from CL silicone hydrogel and discontinuity or even abandonment of the CL port in cases with active and progressive neovascularization [8, 10].
– In these cases, injections of subconjunctival antiVEGF agents are recommended in combination with steroid drops or nonsteroidal anti-inflammatory drugs [15, 16]. In severe cases, stem cell transplantation is indicated [17, 18].

Microbial Keratitis Related to CL

The causes of keratitis are CL-induced hypoxia, microtrauma to the cornea, contamination of CL or maintenance solutions. Another cause of keratitis is poor hand hygiene when applying CL, which will cause direct inoculation of microorganisms.

– The risk of this complication is 20 times higher in those with extended wear [22]. Rupture of the epithelial barrier is an important risk factor in complication and has been associated with silicone-hydrogel CL [23, 24].

Management
– Prevention of microbial keratitis is done by washing hands before applying CL, educating and training the patient about the CL port.
– The objectives of microbial keratitis treatment are to control inflammation, to prevent progression and save the eyeball, eradication of the causative microorganism and antibiotic treatment. In severe cases with corneal perforation or endophthalmitis surgical treatment should be indicated.

Bacterial Keratitis

– The annual incidence is estimated at 2/10,000 LC carriers, depending on the CL type. The highest incidence is in silicone-hydrogel CL carriers, especially those with extended wear [25].
– The exact causative microorganisms are not known, but it is assumed that Gram-negative microorganisms would be involved in the occurrence of the complication [26, 27].
– Clinically, the onset is sudden with ocular pain associated with diminished vision and perilimbal congestion. Slit lamp examination reveals corneal edema and the presence of a central or peripheral infiltrate. In severe cases, Tyndall's phenomenon may be present.

Management
– It is recommended to stop the CL port. From the area with corneal infiltration, a sample will be collected for cultures and also from the CL and maintenance solution [28].
– Treatment with broad-spectrum antibiotics will be started to address both Gram-positive and Gram-negative germs. The antimicrobial medication will be adjusted according to the result of the antimicrobial biogram. Topical treatment with fluoroquinolones is initiated or, in severe cases, subconjunctival injections or general treatment with broad-spectrum antibiotics will be associated [60].

Keratitis with Acanthamoeba

– It is a keratitis produced by a protozoar—*Acanthamoeba*, most often generated by contamination of CL or maintenance solutions.
– In prosper countries, the frequency of this keratitis is 1–33 cases per 1,000,000 LC-carrying patients [29]. Eighty percent of Acanthamoeba keratitis occurs in those with soft LC and only 12% in LCRGP carriers [30].

- The main risk factor is CL itself. The access of the protozoar to the CL box is made by air or water, if the box is not cleaned properly and regularly, infecting the CL. The greatest risk is for soft CL wearers using universal solutions because Acanthamoeba is predominantly attached to the hydrophilic part of these lenses [30].
- The onset of keratitis with Acanthamoeba is sudden with photophobia, decreased visual acuity and eye pain. The biomicroscopic examination reveals palpebral edema, epithelial defects and a stromal infiltration in the peripheral cornea as a ring [30].
- Diagnosis of complication demand corneal confocal scanning, cultures or special staining. The lack of an early diagnosis facilitates the evolution of the disease with a reserved functional prognosis [31].
- Prophylaxis of keratitis with Acanthamoeba consists of using appropriate maintenance solutions for CL cleaning and not tap water, the CL box should be washed by rubbing and left to dry, and the lens box should also be changed every 3 months [32]. The best solutions for disinfecting CL remain those with hydrogen peroxide [33].

Management

- Treatment of the complication is topical with antimicrobial agents with which we can obtain an applicable concentration at the place of infection [32]. The most effective treatment against Acanthamoeba is with Chlorhexidine [30, 34]. Other drugs such as neomycin, paromomycin, voriconazole, miconazole, and imidazole/triazole may also be used. The failure of drug treatment requires surgical treatment such as perforating keratoplasty.

Fungal Keratitis

- It is a severe keratitis caused by different categories of fungi, in connection with the CL wear.
- Twenty-one percent of fungal keratitis cases were diagnosed in CL carriers [35]. Other studies have reported only an incidence of 10% [36].
- The primary risk factor was CL, with the risk increasing in those with extended port [35]. The risk is higher in those with prolonged intake of CL hydrogel compared to carriers of CL silicone hydrogel. LCRGPs have the minimum risk. Furthermore, eye trauma especially with vegetables, topically applied corticosteroids or other systemic immunodepressant illnesses can cause this keratitis [37, 38].
- The most common causative fungal agents are Candida, Fuzarium and Aspergillus [38, 39].
- The onset of complication is sudden with severe eye pain and decreased visual acuity. Biomicroscopic examination reveals a gray stromal corneal infiltrate with poorly delineated edges. Often is also present the hypopion in the anterior cham-

ber. Satellite lesions may also be present. The diagnosis must be confirmed by antimicrobial tests.
– Confocals; it lamp examination may be useful in differentiating the disease from other causes, as well as for observing the evolution under treatment [40, 41].

Management
– Treatment is topical and includes natamycin, amphotericin B, voriconazole, and miconazole [38]. In severe cases, general antifungal treatment is required. In case of failure of drug treatment or when there is a risk of corneal perforation, surgical treatment (debridement, superficial keratectomy, perforating keratoplasty) will be recommended.

Giganto-Papillary Conjunctivitis

– Giganto-papillary conjunctivitis is also called CL-induced papillary conjunctivitis, being the most common complication in CL carriers [42].
– It has an incidence rate of 1.5–47.5% [43, 44], with a frequency of 4.6% in carriers of CL silicone hydrogel [45]. The explanation lies in the greater mechanical irritation of CL silicone hydrogel compared to CL in hydrogel [46]. There was a decrease in the incidence of complication in carriers of disposable CL [47].
– The greatest incriminated risk factor in the appearance of this complication is CL type or material [48]. It is more common in soft CL (85%) compared to rigid CL (15%) [48–51]. Other risk factors are mechanical trauma, history of allergy and atopy [52].
– Patients complain of stinging, foreign body sensation, decreased tolerance to CL wear, conjunctival congestion, excessive CL mobilization and moderate mucous secretions. Slit lamp examination reveals hyperemia and papillae located in the superior tarsal conjunctiva [47, 52, 53].

Management
– In mild cases, frequent use of lubricating eye drops is recommended. In bilateral and generalized cases, it is recommended to discontinue the CL wear until symptoms disappear or the CL will be changed. If symptoms do not disappear, indicate the disposable CL wear. In renitent cases, mastocite cell stabilisers (sodium cromoglycate 2%, Naabak) or antihistamines (antazoline hydrochloride 0.5 mg or olopatadine HCL 0.1%), may also be associated [54, 55].

Arcuate Superior Epithelial Lesion

– It was first described in 1970 as a complication related to the soft CL port. It is also called superior arcuate keratopathy. It was not highlighted in the case of RGP and PMMA lenses [56].

– The incidence of complication among soft CL carriers is very low, 0.2–8%. The extended port, including CL silicone hydrogel with increased DK/t will increase the incidence of complication. The incidence was similar at the extended wear of CL in hydrogel and extended port of CL in silicone hydrogel generation 1 [57, 58].
– Risk factors for this complication are lens design, material properties, and corneal shape. Patient-related factors are: males, presbyopia, tight upper lid protrusive cornea. CL-linked risk components are represented by hydrogel CL with high rigidity or increased material thickness, CL with single curvature [58].
– The lesions begin at the level of the upper cornea, in the 2 mm sector of the upper limbus, after 8 weeks of wearing new CLs or when changing the old ones. The lesion is white, associated with an irregular epithelial deficiency that retains the dye. Some patients are asymptomatic, others complain of foreign body sensation [56–58].

Management

– Discontinuity of the CL port until corneal healing will be recommended. Then, they can wear the old CL. If the complication reappear, CL of another material or design should be indicated [56]. Sometimes there is even a need to change soft CL to CLRGP.

Contact Lens Wearing Complications

Corneal Edema

– It is the most severe cause of decreased visual acuity and is due to corneal hypoxia. It can be caused by CL with a low DK, in the case of a decentered or immobile CL.
– It is highlighted by slit lamp examination, where edema is observed in the central part of the cornea after CL removal.
– In all cases, it will be recommended to change the CL to a lens with a higher Dk/t. Some cases require switching to glasses [59].

Deposits

– Deposit formation is commonly seen in soft CLs, in extended ports, or in spring with the onset of allergies. They must be removed with maintenance solutions or switched to a disposable CL mode.

Contact Lens Damage

– Scratches on the surface of CLRGP are not disturbing and do not disturb vision. The deep ones reduce visual acuity and cannot be removed.
– Soft CLs can break through faulty lens handling. In these cases, it is recommended to replace the lens with a new one [59].

Therapeutic Contact Lenses

Therapeutic contact lenses (TCLs) are indicated to treat specific situations in order to reduce pain, facilitate scarring, improve hydration, provide support and protection, or act as a reservoir for drugs. They are usually soft CLs, but they can also be CL RGP or scleral.

TCL Indications

Indications for Pain Relievers

- It is the most common indication for wearing TCL in eye diseases that create eye pain such as: bullous keratopathy, filamentous keratitis, superficial Thygeson punctate keratitis, upper limbic keratoconjunctivitis and band keratopathy.
  – *Bullous keratopathy* associated with chronic corneal edema generated by endothelial dysfunction, which results in impregnating fluid into the corneal stroma to form characteristic bubbles. It is accompanied by pain and eye irritation by rupturing bubbles and exposing superficial corneal nerve endings. It occurs more frequently in the elderly, predominantly in women. It may occur during the course of Fuchs endothelial dystrophy or after cataract surgery on an eye with few corneal endothelial cells. The use of CL is to relieve pain and prevent neovascularization from occurring, especially if the patient is suitable for corneal transplantation [60]. Usually, soft CLs are used to protect the exposure of nerve endings and can flatten bubbles, reducing them to epithelial edema [59]. Eye pain disappears with TCL placement, but the course of disease is not influenced and pain returns with TCL removal [61, 62]. May be associated with instillations of hypertonic sterile solution with 5% sodium chloride (Edenorm, Biiosoft) 4 times/day to reduce corneal edema and improve vision [63–65].
  – *Filamentous keratitis* commonly occurs in dry eye syndrome (e.g. rheumatoid arthritis). The filaments consist of desquamated epithelial cells and mucus adheres to the cornea. The role of TCL is to diminish the evaporation of existing tears [66]. Before applying TCL, treatment with artificial tears in the form

of eye drops should be followed. All filaments must be removed before applying TCL and followed treatment with artificial tears. Instillations with Acetylcysteine with mucolitic role can be associated [59].

– *Thygeson's superficial punctate keratitis and superior limbic keratoconjunctivitis* are other indications for the use of TCL [67, 68]. The superficial punctate keratitis is distinguish by small, granular, gray lesions which do not retain fluorescein. The conjunctiva is not affected, but the patient complains of pain associated with a white eye. The disease evolves with exacerbations and remissions. Topical steroid treatment relieves pain, as does closing the eyelids or applying on an TCL.
– *Upper limbic keratoconjunctivitis* is a chronic inflammation that occurs in middle-aged women and may be associated with thyroid disease. The superior bulbar conjunctiva is hyperemic and there are papillae in the limbic region. The eye has reduced tear secretion. The initial treatment is with topical lubricants associated with TCL, which will separate the tarsal surface from the bulbar conjunctiva increasing comfort [59].
– *Band keratopathy* is a degenerative disorder of the cornea, generating a calcified band on the superficial cornea at the level of the palpebral slit. Discomfort can be eliminated by using TCL.

Indications for Healing Purposes

- *Epithelial corneal dystrophies*(*Reis-Buckler, Meesman and Cogan*) there is a reduced attachment of the epithelium to the corneal stroma causing corneal erosion. TCL wear promotes healing.
- *Relapsing corneal erosion syndrome* can be generated by previous causes or stromal distrophies. They can occur months or years after injury. Meibomian gland disease has been associated with relapsing erosion syndrome due to modifications in the structure of the tear film [69]. In these situations, the extended wear of the TCL is required. TCL will be used after erosion treatment. The TCL will be left in place for 3–4 months until a new basement membrane forms in combination with topical lubricant treatment. If recurrence occurs, therapeutic photokeratectomy will be indicated [70].
- *Persistent epithelial defects* (*DEP*) secondary to epithelial abnormalities, stem cells or ocular surface are another indication for TCL [59].

  Eye burns can induce DEP. Those with bases have a poorer prognosis than those with acids, due to faster penetration of bases into tissues. TCL will be used if topical treatment with cycloplegics, antibiotics and epithelials does not work. Application of silicone-hydrogel TCL can reduce corneal damage and tissue loss due to collagenase action. If after 2 months of port there is no improvement, an amniotic membrane or limbic stem cell transplant will be applied.

In the case of trophic corneal ulcers associated with persistent epithelial defect, the use of soft CLs with high oxygen permeability can facilitate ulceration healing and prevent the occurrence of secondary stromal ulceration [71]. Peripheral ulcerative keratitis is usually associated with autoimmune mechanism and mediators of inflammatory nature, which destroy collagen in the corneal stroma, thinning the cornea. Using soft CL in such cases protects corneal healing and prevents subsequent melting by facilitating the formation of stromal neovascularization.

- *Corneal irregularities*. The use of TCL in such cases is for pain relievers, replacing the abnormal ocular surface and sometimes can just improve the vision.

Indications for Protective Purposes

- The use of TCL is indicated in case of preventing desiccation generated by corneal exposure in trigeminal or facial nerve damage, trauma caused by changes in palpebral statics, orientation abnormalities of eyelashes or environmental factors (dust).

  In temporary paralysis of cranial nerves, soft CLs will be used, but in definitive ones, scleral type will be indicated. Despite the type of TCL used, the patient will need to be checked due to the increased risk of infection. If no improvement occurs, partial tarsoraphy or insertion of a gold plate into the palpebral thickness should be performed [71].

- In changes of palpebral statics (entropion, ectropion) or the presence of trichiasis, supple silicone-hydrogel TCLs can be used until surgery.

  In patients working in dusty atmospheres, silicone-hydrogel TCL can be used to prevent corneal erosions caused by rubbing the eyelids.

Indications for Hydration Purposes

- *Dry eye syndrome* is a frequent condition of the anterior segment, characterized by discomfort, burning sensation, eye pain, photophobia and recurrent blurred vision [72]. The existence of a normal tear film is a prerequisite for maintaining the good condition of the ocular surface and preventing its deterioration [73].

  There are a number of risk factors that can compromise the ocular surface, such as: low humidity, excessive wind or dust, allergies, high temperatures, air conditioning, old age, excessive computer use, nutritional or metabolic deficiencies, topical antiglaucoma medication with preservatives [74]. Patients most exposed to dry eye development are those with ocular pemphigoid, Sjögren's syndrome, lupus, blepharitis or changes in palpebral statics [75].

Treatment of dry eye consists of the administration of artificial tears to protect the ocular surface, with a rate of administration of 9 times/day, in severe cases [76–78].

In these cases, TCL with moisturizing macromolecules will be used that will greatly improve patient comfort, preventing dry eye symptoms generated by prolonged TCL port. Currently, there is disposable TCL: *Focus Dailies* (*Alcon*), Dailies Aqua Comfort Plus (*Alcon &* Ciba Vision), *1-Day* Acuvue Moist (*Johnson* & Johnson), *and* Fusion *1 day* (*Safilens*). Studies has shown that the release of moisturizing macromolecules has the advantage of being evenly distributed throughout the ocular surface, increasing efficacy. Thus, polyvinylalcohol, polyvinyl pyrrolidone or hyaluronic acid were incorporated into the soft CL to reduce dry eye symptoms [77]. In addition, Maulvi et al. [78]. investigated different methods of loading hyaluronic acid onto CL, increasing comfort.

In severe cases of dry eye, tear plug occlusion associated with improved environmental humidity should also be considered.

Indications for Rehabilitation After Eye Surgery

- TCLs can be used after keratoplasty, corneal refractive surgery (photokeratectomy, keratomileusis *in situ*) or corneal *cross-linking* therapy, for antalgic purposes and favoring corneal epithelialization [1]. TCLs can also be used after limbic stem cell or amniotic membrane transplantation to protect the donor epithelium and maintain hydration.
- TCL use is also indicated after perforating, lamellar keratoplasty or keratectomy. Before placing the TCL, it should be checked that the sutures are sealed and buried to decrease the chance of possible ocular contamination.
- In patients with glaucoma where trabeculectomy has been performed and there is a discontinuity in the filter bubble, CL with high water content and large diameter will be used [71].

Indications for Support Purposes

- maintaining conjunctival fornix bottoms

  In eye diseases, such as ocular pemphigoid, adhesions are formed between the tarsal and bulbar conjunctiva, generating eyelid deviations, obliteration of fornixes and corneal exposure. In such situations, large diameter soft CL or scleral CL can be used to maintain fornix bottoms.

- Ptosis

  In case of palpebral ptosis, scleral CL will be used to support the upper lid

- Corneal erosion or perforation

  Small corneal perforations (corneal wounds, perforated ulcers) can be treated with TCL as a temporary solution to maintain the anterior chamber until amniotic membrane coverage or eventual corneal transplantation. In some situations cyanoacrylate glue can clog the perforation or wound, and TCL is placed over to reduce discomfort [79].

Indications for Delivering Drugs

It is stipulated that TCLs can constitute a drug delivery system, due to the extended wear compared to drugs [80]. Drug delivery techniques include immersion, molecular fingerprinting, drug incorporation in the form of nanoparticles, polymeric ion ligand systems, and surface fluid technology [81–83].

CL can be saturate in the drug before application to the ocular surface or applied to it before instilling a drop. CLs being hydrophilic can be addicted for long-term release of medication on the ocular surface [83, 84]. CL of charged particles have colloidal particles (especially liposomes) inserted in them for sustained release. The other ways are promising methods of drug delivery.

Possible indications in this regard are the prophylactic release of antibiotics, especially in the extended wear.

Contraindications of Therapeutic Contact Lenses

Although TCLs have many indications, there are also contraindications. Absolute contraindications are infectious keratitis, corneal anesthesia, exposure keratopathy with lagophthalmia and paralysis of ocular motility, poor eye hygiene or difficulties in presenting to controls. A relative contraindication is diabetes mellitus, severe dry eye syndrome and anesthetized corneas [85].

Types of Contact Lenses for Therapeutical Purpose

- Silicone-hydrogel CL because of their high transmissibility to oxygen are useful as TCLs and are used in various situations [86].
- RGP CL are used after perforating keratoplasty to reduce astigmatism, the cornea being stable.
- Scleral contact lenses are useful in dry eye syndrome, Stevens-Johnson syndrome and cicatricial ocular pemphigoid, cranial nerve paralysis VII with lagophthalmia, and corneas with anesthesia.

Adaptation of Therapeutic Contact Lenses

When placing a TCL, avoid touching the posterior surface of the CL to the eyelashes, to prevent the circulation of microorganisms or foreign bodies on the ocular surface. During the TCL period, it is well combined with topical antibiotic treatment. The patient will be examined 24 h after CL placement, then 1 week, 1 month and then 3 months after prescription. TCLs should also be changed every 3 months.

Complications of Therapeutic Contact Lenses

- Infectious keratitis is the most serious complication. An Australian study established the incidence/year of complication in carriers of LC 1:10,000 [87]. Despite the high oxygen transmissibility of silicone-hydrogel CL, the incidence of complication was higher in those with extended wear compared to those who removed their lenses in the evening [87]. The lowest incidence was recorded with CL RGP [87]. For this reason, prophylactic use of antibiotics is recommended in case of extended wear CLs. Low hygiene, extended wear and low oxygen permeability are at risk for an increased incidence [88]. The most common etiological agent is *Pseudomonas aeruginosa.* Others are represented by *Staphylococcus*, *Streptococcus*, *Serratia* and *Acanthamoeba.*
- CL hydrogel with low transmissibility to oxygen can induce corneal hypoxia if used as an extended wear. Signs of corneal hypoxia comprise epithelial and stromal edema with new vessels on the cornea and endothelial problems [89].
- TCLs can also induce allergy or inflammation. Papillary conjunctivitis, inflammatory reaction and in difficult cases Tyndall phenomena or cellular reaction may occur [90].

Correction of Astigmatism with Contact Lenses

– Astigmatism is a refractive error characterized by a deviation from spherical curvature, which results in distorted images, as light rays are prevented from meeting at a common focus. Most forms of astigmatism are easily corrected. One option is correction with cylindrical or spherical-cylindrical aerial lenses depending on the type of astigmatism. CLs are another excellent option in correcting moderate astigmatism. Sometimes CL comfort is superior to the aerial lens due to its wide field of view, clear vision and no aberrations from the aerial lens [1].
– For the correction of astigmatism, toric soft CL, CLRGP and hybrid CL can be used.
– For the correction of astigmatism up to ± 2.75 diopters (D), toric soft CL may be recommended, which is often the best solution in correcting astigmatism. The

special shape of toric CL creates different refractive powers that focus light rays on both vertical and horizontal planes. They can correct both corneal and lenticular astigmatism. These lenses have a thicker area that does not allow the CL to rotate when placed on the patient's eye, thus providing vision stability.

– CLRGP may be used above ±2.75 D. This type of lens replaces the deformed surface of the cornea with their smooth posterior face, focusing light on the retina. Because these lenses have a smaller diameter than soft CLs, they require an adaptation period. Adaptation must be done correctly and thoroughly. They are more expensive compared to soft CL.
– Hybrid LCs combine the option of toricity with that of CLRGP. They have in the center a permeable gas material, which is surrounded by a periferous area of silicone-hydrogel or hydrogel. They offer a very good view similar to that offered by CLRGP, at the same time as the comparable comfort of soft CL. They have a thinner edge than CLRGP so the risk of lens loss is much lower in different activities [71].

Keratoconus Correction with Contact Lenses

– Keratoconus is a bilateral, non-inflammatory, progressive corneal dystrophy, defined by its deformation and thinning, with the appearance of irregular astigmatism and decreased vision. It usually begins at puberty, with an increased rate of progression in the second decade of life [91].
– In the initial stages, astigmatism is corrected with aerial lenses. Patients who have affected only one eye or visual acuity is less reduced will continue to wear the glasses. Those whose vision is not correctable with aerial lenses will be indicated CL. The categories of CL used for keratoconus correction are: CL soft-standard, Kerasoft 3 CL, CL RGP, Rose K and Piggyback system.
– In the initial stages, astigmatism is small and soft toric CL may be recommended. Corrected visual acuity may be less good than that corrected with CLRGP, but sufficient for the patient's needs. In initial and moderate keratoconus, better visual acuity can be achieved using CL Kerasoft 3. CL Kerasoft 3 (Ultravision, UK) are of two types: hydrogel and silicone-hydrogel. These CLs are marked with a laser at 6 o'clock and have a toric design on the front surface, containing 74% silicone-hydrogel. In this regard, they will provide good vision and increased comfort to the patient. Studies have shown that when wearing these lenses, the complications induced by them are lower compared to those caused by lenses with the same silicone-hydrogel content [84].
– For better vision, CLRGP (*Softperm-Ciba Vision*) can be used, which are made of a rigid hydrophobic material. These lenses form a system consisting of CL, tear film and cornea to correct astigmatism, reduce aberrations, offers better vision, and manage disease progression through the so-called "shaping" effect [92, 93]. Although the benefits of CLRGP are well known, there has been an

increase in the number of complications [92]. Mechanical grating induced by direct contact between the lens and the anterior cornea, low patient assent with controls, and inappropriate management of RGPCL cause structural deterioration of every corneal layer, affecting visual acuity and disease control in these patients [94].

- Contact lens Rose K (*Nova Contact Lens*) is manufactured specifically for keratoconus. It has a smaller diameter of the optical area to decrease stiffening at the level of the middle periphery and three peripheral curves, which decrease progressively. The lens is manufactured in such a way that the size of the optical zone decreases as the curvature of the base increases and peripheral clearance can be altered [71].
- The piggyback system involves putting a soft silicone-hydrogel CL on the cornea, over which an RGP lens is inserted. This way of correcting keratoconus astigmatism can be considered in certain cases, but the drawback is that the patient has to manage two categories of CLs.

Contact Lenses After Corneal Transplantation

- After corneal transplantation there is an altered profile of the cornea. The matching of the donor graft may be inappropriate to the host cornea, or the graft may move and the graft-host junction is high. Post-keratoplasty perforating astigmatism may occur due to different tensions between the sutures that hold the graft in place [59]. CL adaptation will only be done when there is an intact corneal epithelium. Some surgeons prefer to wait until the sutures are removed. If sutures are present, a rigorous examination of them must be carried out to be sure that there are no suture slippages, their lack or rupture facilitating infection after applying the CL.
- RGPCL or hybrid lenses are most commonly used in these situations due to the high degree of astigmatism induced by the surgical procedure.
- Spherical or aspherical RGPCLs can be easily adapted and provide good vision. If the donor cornea is curved, the lens adapts and centers well. If the donor cornea is flattened, a larger diameter lens will have better stability. The junction between host and graft should be closely monitored. It is often irregular and protruding and we need to make sure that the lens does not press on this area. The lens will be adapted so that it has adequate mobility [59].
- Hybrid CLs have been adequately addicted to correct astigmatism after corneal graft, although they have low oxygen permeability. Adaptation should be made using a lens as light as possible. It has to be checked if the hybrid lens does not cause erosion at the junction between host and donor cornea.

Orthokeratology

- Orthokeratology is an alternative method of temporary correction of refractive errors by modifying the curvature of the cornea [95]. Modern orthokeratology uses lenses made of rigid materials with reverse geometry for a better modification of the corneal shape [96]. Myopia is the most frequent indication of orthokeratology lenses.
- Great accomplishments have been made to prevent myopia progression in children to high myopia knowing its severe complications [97]. A number of clinical studies have proven that orthokeratology, among other newly designed CLs, manages to decrease the progression of myopia [98]. By providing good vision without correction during the day, it has become a particularly popular corrective alternative among children.
- With increasing users of orthokeratology lenses at night, possible complications have posed many problems. Thus, in a retrospective multicenter study, a frequency of microbial keratitis was estimated at 7.7 cases per 10,000 patients [99]. The most common complication was corneal erosion [100]. High myopia at initial lens adaptation is associated with the degree of corneal epithelium discontinuity [101]. In chronic lens wearers, a reduction in basal secretion of tears and instability of the tear film were detected [100]. No endothelial lesions were found in patients with orthokeratology [102]. A number of studies have demonstrated a decline in the central thickness of the cornea (at the level of the epithelium) and an increase in peripheral thickness (both at the level of the epithelium and stromal components) [102].

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Chapter 9
Ophthalmological Pathology and Medical and Surgical Management in Eye Disease Cataract

Mihnea Munteanu, Valeria Mocanu, and Alexandra Preda

Abstract In this chapter the authors describe a very frequent ocular disease—cataract, which untreated leads to visual impairment.

Worldwide, in 2020, in a population aged over 50, the main causes of blindness were: cataract (15.2 millions), glaucoma (3.6 million), corrected refractive errors (2.3 millions), age-related macular degeneration (AMD; 1.8 millions) and diabetic retinopathy (DR; 0.9 millions).

The chapter is composed of an introductory part in which definition, epidemiology, symptomatology of the cataract and anatomy of the lens are presented. The next segment describes the cataract classification, according to the following criteria: etiological, clinical and morphological, degree of opacification, the moment of appearance and evolutionary stage. Presenile/senile cataract is the most common eye pathology associated with decreased visual acuity.

The following part refers to the preoperative evaluation which includes: visual acuity, anterior pole biomicroscopy, refraction and keratometry, intraocular pressure determination, posterior pole examination which can be done with dilated or undilated pupil, ocular biometry and specular microscopy.

Cataract surgery involves removing the cataract and using a lens implant. So, in the final part of the chapter, surgical intervention: anesthesia, surgical technique (for senile cataract and for congenital cataract), postoperative complications and types of intraocular lenses are described.

Keywords Ocular biometry · Intraocular lens · Biomicroscopy · Congenital cataract

Cataract is the partial or total clouding of the lens which consists of protein and water. The arrangement of the proteins maintains the transparency of the lens, allowing light to pass through. With aging, these proteins can begin to break down bringing about the opacification of the lens. Over time, cataracts affect vision quantitatively and qualitatively.

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Cataracts can be uni or bilateral, but the disease present in one eye cannot induce illness in the other. The development of crystalline opacities takes a long time, gradually affecting vision. Cataract progresses until it interferes with daily life, affecting visual acuity.

Epidemiology

Cataract leads to visual impairment, being an important cause of visual loss especially in developing countries. In some cases, it may cause blindness.

Worldwide, in 2020, in a population aged over 50, the main causes of blindness were: cataract (15.2 millions), glaucoma (3.6 millions), corrected refractive errors (2.3 millions), age-related macular degeneration (AMD; 1.8 millions) and diabetic retinopathy (DR; 0.9 millions).

Symptomatology

Decreased visual acuity especially in low light
The appearance of a halo around light sources,
Fading of colors and/or the appearance of a yellow or brown tint around objects
Double vision
Sensitivity to light

Anatomy of the Lens

The crystalline lens is biconvex, transparent, located in the posterior chamber that, together with the cornea, aqueous humor and vitreous body, represents the refractive media of the eyeball. They have the role of refracting light rays and constitute the dioptric system of the eye, with a dioptric power of almost 63 D, of which 10–20 D are provided by the lens and the remaining 43 D are provided by the cornea.

It is located between the iris (anteriorly) and the vitreous (posteriorly), with a vertical diameter of 10 mm, and the anteroposterior diameter of 5 mm.

The lens axis (defined as the line from the anterior to posterior segment) coincides with optic axis.

The circular edge is named as the equator of the lens.

It presents two faces: the anterior face and a posterior one, which rests on the hyaloid fossa of the vitreous body, to which it is bound by a ligament.

The lens is structured in: capsule (outer layer), epithelium and fibers (lens interior). The epithelium cells, situated between the capsule and the fibers outer layer,

are only on the anterior area. The lens is avascular, without nerves or connective tissue.

The crystalline capsule is represented by a transparent basement membrane. Synthesized by the lens epithelium, it consists mainly in sulfated glycosaminoglycans and type IV collagen. The structure of the capsule is very elastic, allowing a more spherical shape to the lens when not under the influence of the ciliary zonules (suspensory ligaments). The thickness of the capsule ranges from 2 to 28 μm. Near the equator is the thickest area and the thinnest to the posterior pole.

The lens epithelium located between the fibers and the capsule, is cuboidal. The role of these cells is to regulate the homeostasis. Nutrients and ions from the aqueous humor enter the lens. The Na+/K+-ATPase pumps have the role to maintain the volume and osmotic concentration. The pumps keep the water and the flow through the poles lens with the exit on the equatorial area.

The lens fibers consist from transparent, thin and long cells with diameters that ranges from 4 to 7 μm and lengths to 12 mm. The fibers are connected by gap and interdigital junctions. The lens fibers extend in horizontal section in concentric layers from the posterior to the anterior pole. On the equator is located the center of each fiber. The tight fiber layers are named laminae.

The crystalline lens is divided in layers according to the fibers age. From the outside to the inside we identify the following structures: outer cortex, adult nucleus, fetal nucleus, embryonic nucleus, the central layer being the oldest. New fibers will be part of the outer cortex. The nucleus has a hard consistency, and the cortex a soft one.

Connecting the ends of the lens fibers form the lens sutures (Y shape).

The relaxing of the ciliary muscle is associated with the stretch of the zonular ligament. The lens becomes flatter with the decrease of its refractive capacity. The ciliary muscle contraction induces the relaxing of the zonular ligament. The lens becomes more convex, increasing its refractive capacity. ***This process is called accommodation mediated by the parasympathomimetic fibers of the oculomotor nerve (N III).***

In the process of accommodation, the anteroposterior diameter increases up to 8 mm; with age, the lens loses its elasticity and plasticity as a result of the progressive sclerosing process.

The crystalline contains: water 65%, soluble and insoluble proteins, ions (Na, K), enzymes, lipids, carbohydrates and vitamins (C, E).

The transparency of the lens is due to soluble proteins called crystallins, and the lens metabolism ensures that its transparency is maintained.

Crystallins represent over 90% of the lens proteins. In the human body we identify three main types: α-, β- and γ-crystallins. Crystallins create high molecular weight aggregates and organize into fibers. The lens will be transparent and its refractive index will increase. In the lens, type β- and γ-crystallins were found. α-Crystallin was reported in different areas of the eye and human body. An important role of type α is to maintain the lens proteins, in order to last a lifetime.

Cataracts can be classified according to the following criteria:

Etiological
Clinical and morphological
Degree of opacification
The moment of appearance
Evolutionary stage

Etiologically, we find the following types of cataracts:

Age-related cataract;

Presenile/senile cataract is the most common eye pathology associated with decreased visual acuity. **The types of senile cataracts: posterior subcapsular, nuclear and cortical are being described below.**

Cataract associated with eye diseases (complicated cataract);

A complicated cataract is defined by secondary lens opacification due to intraocular diseases. In most of the cases**,** intraocular inflammatory such as **anterior, intermediate, or posterior uveitis** induce complicated cataract**.** It is especially disabling in the young age groups due to visual loss and the urgency for cataract surgery associated with its complications. Cataract may be caused not only by the uncontrolled inflammation, but also by the use of steroids. The posterior subcapsular opacities are diagnosed in uveitis, associated mainly with iris and crystalline synechiae.

other intraocular conditions associated with the development of complicated cataracts: **intraocular tumors, pseudocapsular exfoliation syndrome, acute attack of glaucoma** where, secondary to the marked increase in intraocular pressure, we observe the presence of small anterior subcapsular opacities in the pupillary field.

cataracts can also be associated with **refractive errors,** being more common in **high myopia** where we find **nuclear or posterior subcapsular opacities**

posterior subcapsular opacities can also be seen in patients with **Leber's disease or pigmentary retinopathy,** where surgical cure of the cataract will not improve visual prognosis or retinal post-surgery.

Cataract from Some General Diseases

Different studies reported that in diabetic patients, cataract may be diagnosed earlier compared to the non-diabetic patients. For a diabetes mellitus (DM) population aged under 65 years old, the prevalence of cataract was three to four times. In patients over 65, cataract is twice as common. The risk factors for cataract formation are poor metabolic control and longer history of DM. In older patients, cataract becomes irreversible. In young diabetes, a good metabolic control may reverse the process.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy investigated the incidence and risk factors of cataract surgery.

Type 2 DM had a 10-year cumulative incidence of cataract surgery with risk factors such as age and insulin use. Age, severity of DR and presence of proteinuria have been cited as risk factors for type 1 DM.

The Beaver Dam Eye Study observed a relation between diabetes and cataracts, particularly posterior cortical and subcapsular form. Patients with elevated levels of glycosylated haemoglobin had increased risk of cortical and nuclear cataracts.

The Blue Mountains Eye Study reported a relation between DM and posterior subcapsular type, but not for the nuclear form.

In diabetic patients we find two types of cataracts:

"snowflake" cataract (O'Brien), bilateral, with subcapsular opacities, generally seen in young patients with decompensated DM;

presenile/senile cataract—by accelerating lens aging phenomena.

– in metabolic diseases;

Metabolic Diseases Associated with Cataract

At birth: Lowe syndrome, Zellweger syndrome
Newborn (>5 days): Galactosemia, Maternal galactokinase deficiency
Infant (>4 weeks)

(Partial) deficiency of galactokinase
α-Mannosidosis
Hypoglicemia
Sialidosis
Vitamin D deficiency
Lactose intolerance
Hypobetalipoproteinemia and vitamin E deficiency
Lactic acidosis
Maternal galactokinase deficiency

Child

Diabetes
Wilson's disease (Hepato-lenticular degeneration)
Hypoparathyroidism
Pseudohypoparathyroidism
Alport syndrome

Adult

Riboflavin deficiency
Gyrate atrophy with hyperornithinemia
Myotonic dystrophy

Glucose-6-phosphate dehydrogenase deficiency
Wilson's disease is defined as an inherited disorder of copper metabolism. At the ocular level, we find the Kayser-Fleischer ring (periphery of the cornea) and flower-shaped crystalline lens opacities, also at anterior and posterior cortex level.

Traumatic cataract;

ocular contusion: anterior subcapsular opacities (star, rosette)
corneal wound with anterior capsule involvement: complete opacification
prolonged exposure to infrared radiation: punctate posterior subcapsular opacities
chemical burns (especially with bases): cortical lens opacities
intracrystalline foreign body: complete opacification
intraocular foreign body

ferrous: ocular siderosis, anterior subcapsular orange deposits
from copper: chalcose, "sunflower" lens opacification

exposure to electric shocks: crystalline vacuoles in the anterior periphery, then linear anterior subcapsular opacities

Drug-induced cataract (toxic cataract);

The administration of some drugs induces disorders of crystalline transparency, sometimes irreversible.

Drug classes implicated in cataractogenesis

Anti-inflammatory drugs: Aspirin, NSAIDs, steroid anti-inflammatories
Antimalarial medication: Aminoquinolines, Mepacrine
Cardiovascular medication: ACE inhibitors, ß-blockers, Calcium channel blockers, Amiodarone
Diuretics: Furosemide, Thiazides, Potassium-sparing diuretics
Psychotropic medication: Benzodiazepines, Phenothiazines
Miscellaneous: Allopurinol

Posterior Capsule Opacification (PCO)

Posterior capsule opacification, commonest late complication of cataract surgery, has following slit-lamp aspects:

Elschnig's pearls ("fish egg" appearance on the posterior capsule), often found in pediatric patients and young adults. They are located at the border between the remaining inner capsule and the outer one, represented by the proliferation of epithelial cells on the posterior capsule (Fig. 9.1).

the Sommering ring—at the border between the remaining anterior capsule and the posterior one

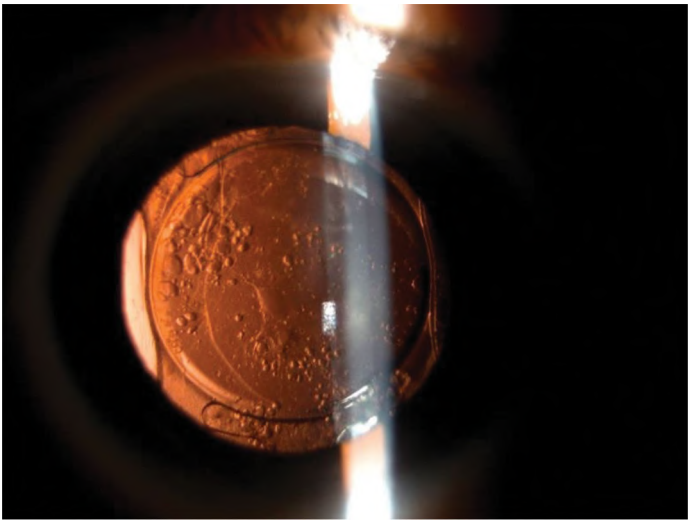

Fig. 9.1 Elschnig' pearls

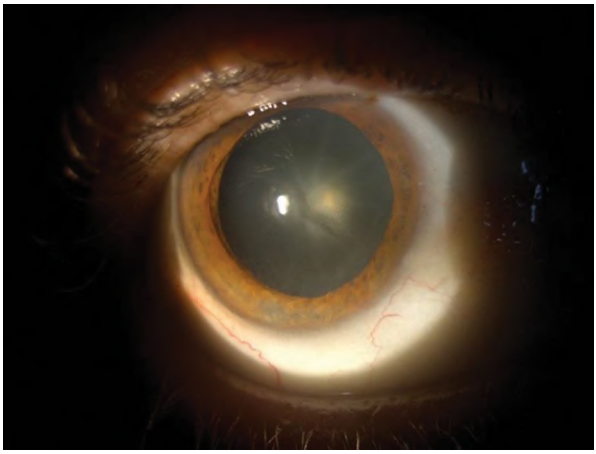

Fig. 9.2 Cortical cataract

capsular fibrosis through the metaplasia of epithelial cells towards myofibroblasts and folding of the posterior capsule.**Clinically and morphologically, cataract can be:**

cortical, the opacities being found in the external layers of the lens. Most of the time, it occurs after the age of 50 with slow evolution towards total opacification (2–3 years). The patient complains of decreased visual acuity with improvement in bright light (Fig. 9.2).

nuclear, with central lens opacification. The symptomatology is a decrease in visual acuity, especially in bright light. In the dark, mydriasis improves the quality of vision by exposing the peripheral lens area. The increase in the lens refractive index induces lens myopia, which improves the patient's visual acuity for near activities (Fig. 9.3).

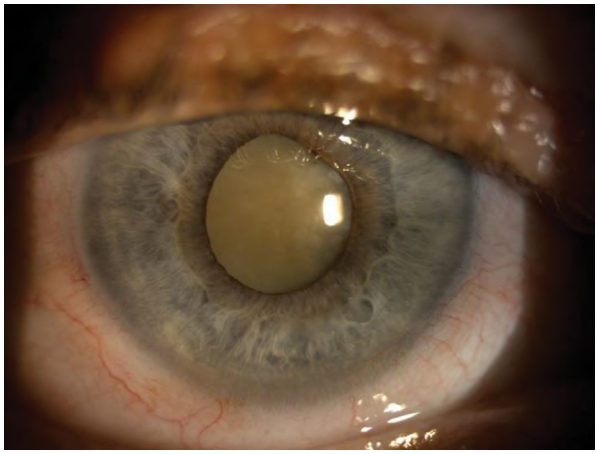

Fig. 9.3 Nuclear cataract

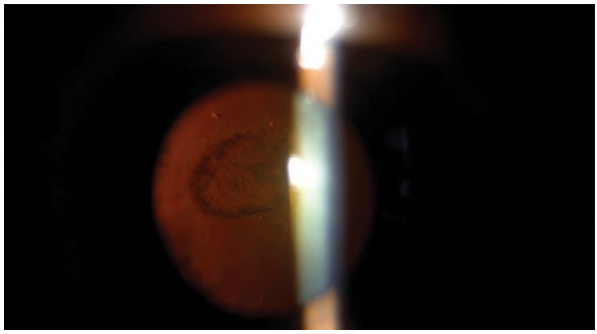

Fig. 9.4 Posterior subcapsular cataract

posterior subcapsular with the involvement of the posterior, central crystalline layers and the rapid decrease in visual acuity (Fig. 9.4).**Lens opacification can be graded depending on the presence of:**

fine opacities (+);
medium opacities (++);
dense opacities (+++);
very dense opacities (++++).**After the cataract occur, we find the congenital or acquired form**

Congenital cataracts are present at birth, but presentation to the doctor and diagnosis may be delayed. However, the congenital nature is confirmed by the morphology: anterior polar, central fetal nuclear, posterior polar, PFV and sutural.

Congenital cataract is hereditary in 8.3–25% of cases. In 75% of the cases, congenital cataract is autosomal dominant (AD), with variable penetrance. This mode of transmission includes Coppock-like cataract, hyperferritinemia cataract syndrome, congenital Volkmann-like cataract and others (aculeiform, sutural zonular, anterior and posterior polar, pulverulent zonular cataracts). Autosomal recessive (AR) forms include different syndromes such as: Marinesco-Sjogren syndrome,

Warburg micro syndrome, Smith-Lemli-Opitz syndrome, Martsolf syndrome, Rothmund-Thomson syndrome, Wilson's diseases, Hallermann-Streiff syndrome and facial dysmorphism. X-linked recessive forms include Norrie disease and Nance-Horan syndrome (NHS).

The etiology of congenital cataract is varied: (Table 9.1**).**

idiopathic: frequently in unilateral cases and in high percentage of bilateral cataracts. Their diagnosis is possible by exclusion.

hereditary:

Norrie disease

Is defined as an X-linked recessive condition due to the mutation of the NDP gene. It is associated with dense congenital cataract, alterations of the retina and vitreous (detachment, folds, hemorrhage). Bilateral retrocrystalline masses with glio-vascular tissue are reported. Extraocular signs are present such as developmental delay and sensorineural hearing loss.

Nance-Horan syndrome

It is an X-linked recessive condition with eye involvement in male patients: bilateral dense nuclear or stellate cataracts and microcornea. Pinna malformations and dental abnormalities are also present. In female gene carriers, presenile cataracts and reduced corneal diameter were reported.

Down syndrome

Cataract is common, with an incidence between 6% and 50%. It is associated with nystagmus, hypermetropia, strabismus or entropion.

Lowe syndrome

It is an X-linked disorder defined by the classic triad: mental deficiency, renal tubular dysfunction and congenital cataract. In some cases arthropathy and muscle dystonia are present. Most of the patients do not exceed the age of 40.

Metabolic:

Galactosemia

Table 9.1 Etiology of pediatric uni- and bilateral cataracts

Bilateral cataract	Unilateral cataract
Idiopathic	Idiopathic
Hereditary (AD)	Traumatic
Genetic and metabolic diseases: Down syndrome, Marfan syndrome, Alport syndrome, Fabry disease	Postrubella
Galactosemia	Ocular anomalies: persistent fetal vasculature, anterior segment dysgenesis
Trisomy 13–15	
Myotonic dystrophy	Posterior lenticonus
Hypoglycaemia	Tumors of the posterior pole
Hypoparathyroidism	
Maternal infections	
Eye abnormalities: Aniridia	
Corticotherapy	

It is defined by increased serum galactose levels determined the mutations in galactose-1-phosphate uridyltransferase, galactokinase (GALK1) or uridine diphosphate 1–4 epimerase. Through an osmotic mechanism, the accumulated galactitol damages the lens—"oil drop cataract". A nuclear cataract usually occurs, but also anterior or posterior subscapular cataract types. If galactose is removed from the diet, initial changes are reversible. Milder forms are reported in galactokinase deficiency with different clinical aspects: jaundice, mental retardation, vomiting, weight loss, hypoglycemia and hypocalcemia.

infectious (toxoplasma, syphilis, herpes, cytomegalovirus and rubella,—TORCH):

Rubella is more commonly associated with congenital cataract. Microphthalmia, chorioretinitis, glaucoma, iris dystrophy, pigmentary retinopathy have been reported. Congenital rubella syndrome is characterized by the triad: hearing loss, cardiac involvement and cataract. Cataract is generally, but not necessarily bilateral. In some cases it may be associated with "salt and pepper" retinopathy. The diagnosis includes ELISA testing for IgM type antibodies for the specific antigen.

anterior segment dysgenesis:

In Peter's anomaly, central corneal opacity occurs and irido- or keratolenticular involvement may be encountered. Other ocular conditions may be present: microcornea, posterior embryotoxon or chorioretinal anomalies. Frequently sporadic cases, others familial show the AR transmission. Anterior chamber lens dislocation, anterior polar or nuclear cataract may occur.

pre-existing posterior capsular defect: Incidence ranges between 2.2% and 6.75%. It is associated with lentiglobus or lenticonus, posterior polar cataract, persistence of fetal vascularity. A total cataract occurs or sometimes differentiated opacities, mainly in the center, with posterior capsule white spots, fish tail sign and anterior vitreous.

Cataract presents different clinical progressive stages: (Table 9.2)

incipient, with insignificant decrease in VA. Frequently, patients complain of the presence of a black, fixed spot in the pupillary field, and the refraction may reveal myopia, which previously did not exist. In some cases, patients mention seeing an object in multiple copies, a phenomenon called polyopia and suggests the presence of crystalline astigmatism.

intumescence with a narrowing process of the anterior chamber produced by the hyperhydration of the lens and secondary increase in its volume.

mature with completely opacified and dehydrated lens.

hypermature or morganian. It is characterized by the reduction of the crystalline volume due to its liquefaction.

Different cataract classification systems have been suggested, from the complex variant by photographic documentation to the simple evaluation of the red reflex with the help of the ophthalmoscope. All clinical classification systems have been

Table 9.2 Morphology of pediatric cataract

Total involvement	Central	Anterior	Posterior	Different localization
Morganian Total Membranous	Central pulverulent cataract Lamellar "Ant-Egg" cataract "Oil Drop" cataract Cortical cataract Coronary cataract	Anterior polar Anterior pyramidal Anterior lenticonus Anterior subcapsular Punctate Placoid	Mittendorf dots Posterior—cortex, lenticonus, subcapsular	Sutural Coraliform Punctate opacities Feather appearance Primitive vitreous hyperplasia

used most of the time by researchers, ophthalmologists encountering certain difficulties in accurately applying a complex scoring system.

Preoperative Evaluation

The preoperative evaluation of cataract patients varies according to the age of the patient.

Ideally, visual acuity is tested, **anterior pole biomicroscopy is performed, refraction and keratometry are measured, and posterior pole examination which can be done with dilated pupil or without it.**

Cataract surgery involves removing the cataract and using a lens implant.

To determine the value of the needed lens implant, an investigation called ocular biometry is required.

Another important investigation in the evaluation of the cataract patient and possible postoperative complications is **specular microscopy.**

Ocular Biometrics

In order to determine the ocular biometry, several anatomical measurements of the eye are performed. Axial length, keratometry (posterior and anterior corneal astigmatism) and anterior chamber depth are determined by the same device. These biometric measurements are very important for selecting the correct lens implant power to obtain the targeted refractive result after the surgery.

Eye biometry is crucial before cataract surgery.

Two procedures are currently used: ultrasound (direct contact or immersion) and optical biometrics. Due to certain disadvantages of ultrasound biometry, **optical biometry has become the best and most used procedure in ocular biometry.**

Ultrasound biometry is an invasive procedure that implies the use of topical anesthetics and direct contact with the cornea, both of which can produce some degree of discomfort to the patient. Furthermore, this measurement technique may involve errors because of the excessive compression of the ultrasound probe on the cornea. Immersion avoids compressing the cornea, but has less control over alignment, so it can produce different results. In ultrasound biometry depending on media and/or optical existing conditions, the ultrasound speed must be adjusted. e.g. pseudophakic eyes and silicone oil.

The techniques underlying **optical biometry** are partial coherence interferometry and swept-source OCT (optical coherence tomography). The interference between the light reflected by the tear film and the one reflected by the retinal pigment epithelium produces a signal, which is used in partial coherence interferometry.

Optical biometry is an automatic process and is considered a more reliable test due to the fact that it does not depend on the experience of the examiner, whose only task is to align the device to the patient's eye.

In eyes with dense cataract or media opacities, optical biometry has its limitations regarding the ability to measure axial length and anterior chamber depth.

Emmetropia is the ideal result targeted in patients undergoing cataract surgery. However, under certain circumstances, target refractions of different values, myopia, hypermetropia can be considered.

Axial length can be measured using optical or ultrasound methods. The distance between the anterior surface of the cornea and the retinal pigment epithelium is called axial length. Axial length is a very important parameter used in the formulas for calculating lens implant power. It can influence the value of the lens implant from almost 2.5 to 3 times, more for short eyes than for longer ones.

It can be determined using ultrasonography (immersion or contact) or optical methods. The ultrasound principle is based on mechanical waves to calculate how much time is needed for a pulse to get from the cornea to the retina. Sound travels at different speeds depending on the environment, a lot more in the lens and cornea (1641 m/s) and less in the aqueous and vitreous layer (1532 m/s).

Even though constant A is called a constant, in fact it is a variable which depends on several factors, such as: the material, the type and position of the lens implant, incision technique, incision position;

The GAIN used in contact biometrics is measured in decibels (dB). It is defined as the electronic amplification factor of the sound waves received by the transducer. The basic parameters are around 70–75%. The parameters can be increased where large echoes are inadequate (dense cataracts and ocular opacities, high myopia). It is low when artifacts are encountered close to the retinal vertices (silicone-filled eyes and in pseudophackic patients).

Over time, formulas for calculating lens implant power have evolved. They can be classified based on their derivation (theoretical, regression analysis or combination) or in accordance with their generational evolution. By derivation, the theoretical formulas are obtained by applying geometric optics to schematic and reduced eyes using different constants. After a period of time, regression analysis applying

the real postoperative outcome of implant power as a function of the variables of corneal power and axial length were derived. Sanders, Retzlaff, and Kraff introduced the SRK formula that has been commonly and frequently used. Although it has now been replaced by the newer generation formulas, it is still useful tool for understanding the relationship between the variables and the constant A with the power of the lens implant.

Corneal power (K) is the second most important factor in determining lens implant power. Changes in K values produce changes in the power of the implant in a ratio of almost 1:1. It can be determined by either topography or keratometry, optical biometers perform these measurements automatically.

Lens Implants

Types of Materials

The materials from which implants are made have been improved over time, becoming more flexible and biostable. The first lens implants were made of a thermal plastic, a material that has changed over the years but still has some innate restrictions for microsurgery. Today's state-of-the-art acrylic implants offer better characteristics such as plasticity and stability and give surgeons better control during microsurgery.

Polymethyl methacrylate (PMMA)—it was once the standard for excellence. These lenses are less flexible and micro-procedural friendly than newer materials. In some cases, very rarely, certain patients need a material with less flexibility, in which case a PMMA lens may be considered.

Silicone—an older choice used for cataract surgery but inferior to acrylic implants. There are still some rare situations in which due to their consistency, silicone lenses are a good choice for some patients.

Acrylic—today's most frequent choice, because it is easy to bend and ideal for microsurgery. There are different types available, and the choice of implant should take into consideration the patient's eye status, needs and desires.

Types of Lens Implants

Currently, there are two types of lens implants: monofocal and multifocal. In the multifocal category, there are trifocals and extended depth of focus (EDOF).

Monofocal and Toric Monofocal Implants

These lenses have been around the longest and are still the most common. Even though the quality of materials and design continue to improve, the function of the lens remains constant. A monofocal lens implant has equal power in all areas and a single area of sharp focus, produces excellent vision at a given distance.

Toric lens implants have variable powers in different areas of the lens and must be aligned in a certain axis. They are the only ones that can correct astigmatism.

Multifocal: Trifocal Lenses

Multifocal implants were developed to boost the results of cataract surgery. They enhance near vision by dividing light into multiple foci (near, distance and intermediate), which alters the physiology of vision due to light dispersion. Due to this phenomenon, symptoms such as halos, glare and decreased contrast sensitivity may be experienced by the patients.

Multifocal implants refract or diffract, or both, light from an object. This process is made simultaneously in far and near vision, and a part of this light is dispersed. For this reason, they are classified as refractive, diffractive or combined. Also, these implants can be toric or non-toric.

Refractive models produce multifocality through annular zones with various refractive powers and frequently provide adequate intermediate and distance vision; however, sometimes the near vision is not enough for the needs of the patients. They depend on pupil movements, are very sensitive to their centering, can produce glare and halos, and can lower contrast sensitivity.

The diffractive patterns are composed of concentric areas with diffractive microstructures that approach one to another as they move away from the center. They usually provide satisfactory distance and near vision, but intermediate vision may not be sufficient in some situations. They are not so dependent on pupil movements but affect contrast sensitivity even more.

Extended Depth of Focus EDOF

Extended Depth of Focus (EDOF or EDF), or *Extended Range of Vision* is a current technology of multifocal lens implants that appeared relatively recently. Unlike multifocal intraocular lenses utilized in the treatment of presbyopia, EDOF lenses function by creating a single, elongated focal point to improve “field of view” or “depth of focus”.

Preoperative Evaluation in the Case of Congenital Cataract

Depending on the age at which the patient with congenital cataract presents to the doctor, the preoperative evaluation can be performed completely or partially. In some cases, general anesthesia is required for the examination of the anterior pole, the evaluation of the stage of the cataract, the posterior pole, the measurement of keratometry, the determination of the anteroposterior axis of the eyeball and the performance of ocular biometry.

Examination of the newborn with congenital cataract is challenging. Visual acuity is impossible to test, so eye examination is the only method of assessment. There are certain clinical landmarks that indicate the stage of the cataract evolution and the timing of surgery. The density of the cataract can be evaluated by analyzing the red reflex from the retina and the visibility of the fundus elements, using direct or indirect ophthalmoscopy. The density, morphology of the cataract, the presence of nystagmus, strabismus and the association with other eye diseases indicate the stage of the cataract and the indication for surgery.

There are mobile devices for measuring keratometry, and the preferred biometry method is immersion.

The difficulty of obtaining the value of the lens implant in pediatric patients consists both in attaining the values necessary for the biometric calculation and the fact that we cannot estimate the growth of the eyeball over the years. There are some scientific data that suggest the growth rate of the eyeball. Until the age of 2 years, the axis grows by 6 mm, at the age of 2–5, it grows by 0.4 mm, between 5 and 10 years old, it grows by 1 mm, and between 10 and 15 years old, the growth is insignificant.

The postoperative target until the age of 10 years is low hypermetropia.

Preoperative Evaluation of Cataract in Adult Patients

The determination of visual acuity, intraocular pressure and refractokeratometry are standardized and provide information connected to cataract grade.

Biomicroscopy of the anterior pole is an essential part of the mandatory examination to highlight the type of cataract and identify possible contraindications for cataract surgery.

Examination of the posterior segment of the eye, when possible, is important for the diagnosis of other eye pathologies, which may influence the visual result after surgery.

Ocular ultrasound is a useful investigation to rule out pathologies such as intraocular tumors, retinal detachment, vitreous hemorrhages that can complicate cataract surgery. This investigation is especially useful in the case of very dense cataracts, where the fundus cannot be assessed.

Ocular biometrics.

Risk Factors in the Occurrence of Cataract

Aging
Smoking
Obesity
High blood pressure
Diabetes
Previous eye surgeries
Previous eye injuries or inflammations
Prolonged use of corticosteroid drugs
Excessive alcohol consumption
Excessive sunlight exposure

Surgical intervention: anesthesia, surgical technique (senile cataract, congenital cataract), postoperative complications.

Cataract surgical treatment is recommended when the crystalline eye pathology influences the quality of life and prevents the performance of daily activities.

Indications for surgical intervention are:

The visual function no longer meets the needs of the patient and is affecting his daily activities. By the term visual function, we refer to certain factors such as: visual acuity, contrast sensitivity, color perception, optical aberrations, binocular vision (anisotropy, aniseikonia).

In cases in which postoperatively, the patient will obtain an improvement in visual acuity, impossible to obtain by recommending optical correction.

To visualize the fundus, for diagnostic and/or therapeutic purposes.

In the prevention of cataract-induced complications: phacomorphic or phacolytic glaucoma or phacoantigenic uveitis.

Stages of Surgical Intervention in Patients with Senile Cataract

Anesthesia

Extraction of the cataract with implantation of intraocular lens (IOL)

Anesthesia

There are three types of anesthesia performed for cataract surgery:

1. topical epibulbar anesthesia by applying Oxybuprocaine 0.4% eye drops (most often used for modern surgical techniques with small incisions)

2. regional anesthesia through para-, retrobulbar injections with Lidocaine 2%—10 mL, Bupivacaine 0.5% 5–8 mL;
3. intravenous anesthesia

- **Extraction of the opacified lens can be performed using the following techniques:**
- ***intracapsular***.
- ***extracapsular: classic, through phacoemulsification (modern, mini-invasive technique) or femto laser assisted cataract surgery.***
- Currently, the most used is the **phacoemulsification technique**, which includes the following stages:
  - **Sterilization** of the ocular and periocular area, operating field application, blepharostat fixation
  - **Incisions at 10 o'clock and 2 o'clock** positions using the V lance 15° knife, which may be placed:

    limbic; with risk of iris prolapse and high postoperative astigmatism
    sclero-corneal (tunnel type); minimal postoperative astigmatism, risk of hyphema
    corneal (clear corneal incision); dimensions of 1.9–3.2 mm, minimal post-operative astigmatism, risk of endophthalmitis

  - **Introduction of viscoelastic substances into the anterior chamber**
  - There are three types of such substances:

    high molecular weight (MW) cohesives, used for the capsulorhexis maneuver, IOL implantation;
    dispersive with low MW, but high coverage capacity
    dispersive-cohesive with very high MW and with the properties of both types of substances described above.

  - **Capsulorhexis**: round with dimensions of 5–6 mm.
  - The most used technique for capsulorhexis is the manual one which can be performed with the help of:

    cystotome 26 G, making a small perforation in the anterior capsule, then taking off the capsule clockwise, from the center outwards.
    Special capsulorhexis forceps, easier to perform and with better control.

  - **Hydrodissection:**
  - using a 2 mL syringe with saline or BSS solution and a 22–26 G cannula; separate the cortex from the capsule until the nucleus rotates easily.
  - **Hydrodelineation:**
  - the separation of the nucleus from the cortex is achieved by introducing liquid into the cortex with the appearance of the "golden ring".

- **Phacoemulsification of the nucleus by two methods:**

  chopping (quick chop, stop and chop, phaco-chop) with multiple fragmentation of the nucleus;
  cracking (divide and conquer, chip and flip) with the creation of a deep trench, followed by the fragmentation of the nucleus into four pieces.

- **Removal of the remaining cortex** with the help of irrigation-aspiration probes.
- **Polishing the posterior capsule** with the help of the polishing cannula.
- **Intrasaccular insertion** of viscoelastic substances
- **IOL implantation**
- **Removal of viscoelastic substances** by irrigation-aspiration
- **Administration of cefuroxime** solution in the anterior chamber
- **Hydration** of incision with the help of cannula

Postoperative treatment differs according to the protocols of each medical institution and surgeon's option. Most often we encounter the following scheme:

Antibiotics in the form of eye drops (3–6 times a day) or ***ointment*** (3 times a day)—5–7 days (maximum 1 month) from the fluoroquinolone class (e.g., Levofloxacin 0.3%, Moxifloxacin 0.5%, Ciprofloxacin 0.3% ointment) or aminoglycosides (Tobramycin 0.3% solution or ointment, Netilmicin 0.3%).

Steroidal anti-inflammatories (SAI eye drops) Dexamethasone, 0.1% solution—2 drops × 2–6 times a day, up to 1 month *or* combinations of antibiotics and corticosteroids: Netilmicin/Tobramycin 3 mg/mL + Dexamethasone (1 mg/mL), Dexamethasone 1 mg, Neomycin 3500 IU + Polymyxin B 6000 IU,—1–2 drops × 3–6 times a day, up to 1 month.

In complicated cases, one can also use:

Non-steroidal anti-inflammatory drugs: eye drops (Diclofenac sodium, 0.1% solution 1 drop 3–5 times daily, for 1 month), and/or systemic (Indomethacin 0.025%, 2–3 times a day, 7–10 days)

Mydriatics or cycloplegics (Tropicamide 1% solution, 1 drop 1–3 times a day, for 5–7 days) in selected cases.

Anti-inflammatory steroids in subconjunctival and/or parabulbar injections: Dexamethasone 0.04% solution, 0.5–1 mL, 5–7 days, in selected cases.

Antibiotics administered subconjunctivally and/or parabulbarly and in systemic administration from cephalosporins or aminoglycosides class.

A study published in 2021 reported that a combination of levofloxacin and dexamethasone used for 7 days, followed by 1 week of dexamethasone eye drops, provides similar results to 2 weeks of dexamethasone/tobramycin treatment in order to prevent or reduce inflammation and to avoid infection.

- ***Postoperative monitoring***

The patient will be ophthalmologically followed-up for an initial period of 1–5 days for VA assessment using the pinhole test, for intraocular pressure and

biomicroscopic examination to assess the tightness of the corneal incisions, the anterior pole and the position of the lens implantation.

The patient will receive all the necessary recommendations: the treatment plan, periocular hygiene advice and limiting physical exertion for 1 month.

One month postoperatively, an ophthalmological consultation will be performed with the possibility of recommending optical correction in cases where it is required.

Intraoperative Complications

1. ***Postbulbar injection with anesthetic agent:***
   parabulbar hematoma with ptosis, palpebral hematoma, limitation of eyeball movements. Cataract surgical cure will be delayed.
   perforation of the eyeball producing retinal breaks, hemorrhagic flakes in the vitreous
   strabismus by injuring the inferior rectus muscle

Intraoperatively loss of the capsulorhexis, of the anterior chamber; extension of the capsulorhexis in the periphery; too small capsulorhexis; tear of the posterior capsule with the presence of vitreous in the anterior chamber and the risk of dislocation of the lens in the vitreous; suprachoroidal hemorrhages; Descemet's membrane lesions; iris prolapse.

Postoperative Complications

Early: corneal edema, transient intraocular hypertension, pupillary block, uveitis, choroidal and retinal detachment, endophthalmitis, intraocular lens dislocations, surgical wound dehiscence, intraocular hemorrhages.

Late: cystoid macular edema (Irvine-Gass syndrome), corneal astigmatism, uveitis, endophthalmitis, posterior capsule opacification, retinal detachment, bullous keratopathy (corneal dystrophy), surgery-induced astigmatism, biometric errors.

Peculiarities of Pediatric Cataract

The critical period of eye development is between the ages of 2–6 months, and emmetropization is generally reached by the age of 9 years. However, brain plasticity may extend beyond the first decade of life.

Surgical treatment is recommended for extended opacities (e.g., central opacity greater than 3 mm) to free the visual axis and allow vision to develop.

In ideal conditions, surgery should be performed by 6 weeks of age in unilateral cataracts, and bilateral cataracts by 8 weeks, if possible.

In symmetrical forms, the time period between the surgeries is 1 week. In cases with increased anesthetic risk, the surgical cure can be performed within the same surgical session.

In the case of insignificant opacities (punctate or posterior polar cataract), the child will be monitored periodically.

The technique used in pediatric cataracts is different from that used in adults because children have less scleral and corneal stiffness, the anterior capsule is very elastic, soft lens and well-formed vitreous.

Superior incision is usually made which allows protection of the wound by the upper eyelid and Bell's phenomenon during the childhood years when exposure to trauma is greater.

Both scleral and corneal incisions can be performed, with no important difference in the subsequent development of astigmatism.

The surgical technique consists of aspiration or lensectomy with anterior vitrectomy and posterior capsulotomy.

The corneal incision will be trapezoidal and sutured at the end of the intervention.

Certain difficulties may be encountered when performing anterior capsulorhexis caused by its elasticity.

The use of a capsular dye (Contrast Blue, Trypan Blue) and high MW viscoelastics is recommended in order to provide stability to the anterior chamber.

It has been shown that the *two incision push-pull* technique offers a consistent size of the capsulorhexis.

Multiquadrant hydrodissection (three quadrants at least) is the method of choice in pediatric patients, followed by bimanual lens aspiration.

In order to reduce the risk of developing opacification of the posterior capsule, it is adviced to polish it or the posterior capsulorhexis, which will be smaller than the anterior one, and the implantation of a hydrophobic acrylic foldable implant with a square edge design.

Because of the immaturity of the blood-aqueous humor barrier, in pediatric patients the ocular inflammatory reaction is more severe, with a fibrinous appearance, pupillary membranes, and posterior synechiae.

Topical steroids and cycloplegics will be prescribed. Topical steroids administration will be tapered after 6–8 weeks.

Patients will be re-examined 1 month postoperatively and every 3 months thereafter.

The intervention will be followed by the immediate prescription of optical correction, and amblyopia therapy will begin before the sutures are removed. The patient must wear optical correction and perform occlusive therapy.

In cases of unilateral aphakia, it is advised to wear contact lenses to avoid aniseikonia. The results of the Infant Aphakia Treatment Study show that primary pseudophakic implantation compared with wearing contact lenses for aphakia proved no important difference in final visual outcome in children less than 7 months of age.

In small children, glasses for near vision will be prescribed, and for schoolchildren executive-type bifocal glasses with an addition for near vision.

In pediatric cataract surgery, the most common complication, with or without intraocular lens implantation, is OCP, which can cause amblyopia through visual deprivation. In severe forms, posterior capsulotomy associated with anterior vitrectomy is necessary.

In complicated or traumatic cataracts patients may develop accentuated inflammatory reactions that can induce the formation of posterior synechiae, with pupillary seclusion, closed-angle glaucoma and OCP.

Glaucoma is a complication seen in 10–25% of children. Risk factors are younger age and the presence of microphthalmia. Increased intraocular pressure can be corrected with medication or may require surgery.

Some factors, such as the administration of topical steroids and cycloplegics during the postoperative period, improved surgical techniques have significantly reduced the complication rate.

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Chapter 10
Ophthalmological Pathological and Management in Eye Disease: Glaucoma (Diagnosis and Treatment)

Simona Delia Nicoară, Ana Banc, Ioana Damian, and Iulia-Andrada Nemeș-Drăgan

Abstract **Glaucoma**, the leading cause of irreversible blindness, is classified into two types: open-angle, with aqueous humour (AH) passing freely through the trabecular meshwork (TM) and angle-closure, in which the access of the AH to the TM is blocked. Both types can be primary or secondary to ocular or systemic diseases.

Primary open angle glaucoma (POAG) is a chronic, bilateral, progressive and irreversible optic neuropathy, at least partly related to intraocular pressure (IOP), in which the loss of neuroretinal rim and retinal nerve fibres' layer (RNFL) translates into typical visual field (VF) defects. The cause of POAG is unknown and the clinical picture lacks in symptoms until the advanced disease stages. The goal of treatment is to stabilize disease progression, by reaching a target IOP at which the VF, optic disc and RNFL are stable, with the help of medical, laser and/or surgical means.

Primary angle closure glaucoma has an acute onset with severe decrease of the visual acuity in a very painful red eye, without or with minor previous clinical manifestations. It is an emergency, the delay of medical care leading to vision loss. Once IOP is decreased with medical means, laser and/or surgical treatment is performed. Peripheral laser iridotomy in the fellow eye is mandatory.

Whenever the cause of elevated IOP leading to optic nerve damage can be identified, the **glaucoma** is considered **secondary** and it is treated by addressing the cause.

Childhood glaucoma (primary or secondary) is a relatively uncommon condition in which IOP control is very challenging.

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Epidemiology and Pathogenesis

Epidemiology

Glaucoma is the leading cause of irreversible blindness worldwide, followed by Age-related Macular Degeneration.

There are two types of glaucoma: open-angle (OAG), in which the aqueous humour (AH) passes freely through the trabecular meshwork (TM) and angle-closure (ACG) in which the access of the AH to the TM is blocked. Both glaucoma types can be either primary, or secondary to various ocular or systemic diseases.

The prevalence of primary open angle glaucoma (POAG) is higher than for primary angle closure glaucoma (PACG). Thus, it was established that POAG occurred in 3.05% among people aged between 40 and 80 years, whereas PACG in 0.50% within the same age contingent in a study performed in 2013. These numbers increased by 18% by 2020, totalizing 76 million people, and it is estimated to reach 111.8 million people by 2040, due to the global aging of the population.

Although the prevalence of OAG is higher than that of ACG, it was proved that blindness occurs in 25% of ACG compared to 10% of OAG. According to the data provided by the Early Manifest Glaucoma Trial, the natural rate of progression in POAG was 1.08 dB/year, whereas for pseudoexfoliation glaucoma (PEX), 3.12 dB/year. The natural progression rate of normal tension glaucoma (NTG) was 0.36 dB/year, lower than for high tension glaucoma (1.31 dB/year).

Pathogenesis

POAG Although not all the pathogenetic mechanisms are fully understood, there is certainty that the death of retinal ganglion cells (RGCs) which is at the origin of visual loss, is related to the intraocular pressure (IOP) level which is determined by the balance between the secretion of AH by the ciliary body and its outflow through the TM and the uveo-scleral pathway. The site of IOP increase in POAG is the TM and the effect is translated through the mechanical stress especially at the level of lamina cribrosa (LC), a perforated portion of the posterior sclera through which the RGCs axons exit the eye. LC becomes thinned and displaced posteriorly, with subsequent increase and deepening of the cup, simultaneously with the narrowing of the rim. This remodelling of the LC is the first step in obstructing the retrograde axonal transport with following interruption of delivering essential nutritional factors to the RGCs and their subsequent apoptosis. The compression of the blood vessels nourishing the optic nerve translates into ischemic damage that is added to the mechanical one.

Primary Angle-closure Disease (PACD) The angle of the AC can be closed either by an appositional mechanism or by synechiae. Pupillary block has the main role in most PACDs. Once the pupil is blocked, AH can no longer get into the AC, it accumulates in the posterior chamber determining the increase of pressure within this space. As such, the iris bows anteriorly, crowding the angle of the AC in eyes with narrow angles. Besides this, other morphological factors, such as iris volume and insertion into the ciliary body, as well as the thickness and position of the ciliary body. The higher volume of the crystalline lens, its thickening with age and its more anterior position, combined with pupil dilation, may contribute to the appositional iris to the AC angle. These changes may have a rapid evolution resulting in acute angle closure crisis (AACC), or a chronic one characterized by the repeated and for a long time touching of the TM by the iris with the subsequent development of peripheral anterior synechiae (PAS).

Plateau iris configuration and syndrome defines a condition in which the eye has deep AC, but the peripheral iris is appositional to the angle, as revealed by gonioscopy. The cause of this configuration is represented by the anterior rotation of the ciliary body.

The risk factors for primary glaucoma (open or closed angle) are classified into demographic, systemic and ocular ones.

Demographic

(a) *Age*: older age is a risk factor for both, POAG and PACG.
(b) *Gender*: POAG is more prevalent in men, whereas women are more at risk for developing PACG and AACC.
(c) *Race*: POAG is three times more prevalent in Black and Latino race, whereas PACG is more prevalent in people with Asian ancestry.
(d) *Family History*: if someone has a first-degree relative with confirmed POAG, their risk of having this disease is 9.2-fold higher. There are several genes that explain partially the familial transmission of POAG, such as: myocilin, optineurin, WDR36, CYP1B1 and ASB10. Regarding PACG, there are several genetic loci that in combination with the transmission of anatomic characteristics explain the predisposition to this condition. It was proved that the siblings of Eskimos with PACG had a 3.5 fold higher risk for developing the disease.

Systemic

No systemic risk factor has been identified for PACG.

Systemic risk factors for POAG are:

(a) *Low diastolic blood pressure*: Within this group, it has been shown that only the patients who were treated for systemic hypertension had an increased risk for POAG.

(b) *Diabetes*: every year from diagnosis increases the risk for POAG by 5%.
(c) *Alcohol*, *caffeine and cigarette* are not clearly associated with POAG.

Ocular

(a) *Elevated IOP*: the prevalence of POAG gets higher in parallel with IOP increase. Considering an IOP higher than 21 mmHg as cut-off value for screening and diagnosis of POAG is wrong, as approximately 80% of cases would be missed.
(b) *Refractive status*

Moderate to high myopia is considered a risk factor for POAG, as weaker scleral support favours the progression of glaucomatous optic nerve damage.

Hyperopia is a risk factor for PACG. It has been found that eyes with PACG were 1.00 D more hyperopic compared to non glaucomatous eyes.

(c) *Cornea*

Central corneal thickness (CCT): thinner central cornea is considered an independent risk factor for POAG, as in these eyes IOP is underestimated. Contrary, a thicker central cornea predisposes to the overestimation of IOP.

Small radius corneal curvature is associated with a more crowded AC which is a risk factor for angle closure.

(d) *Anterior chamber depth* (ACD): a shallow AC is a risk factor for PACG. AC was proved to be 0.3–1.0 mm shallower in eyes with PACG as compared to healthy eyes.
(e) *Lens thickness*: 0.2–0.6 mm thicker lenses were found in eyes with PACG or AACC than in normal eyes.

Evaluation and Diagnosis

Evaluation

History

- **Ocular history**: refractive error, ocular trauma or inflammation, prior ocular surgery (e.g., cataract surgery may decrease IOP, refractive surgery by thinning the cornea may lead to falsely low IOP measurements), current and prior ocular medications (especially steroids).
- **Systemic history**: cardiovascular disorders, Raynaud's syndrome, migraine headache, diabetes, thyroid dysfunction, sleep apnea or other respiratory disorders, other chronic disorders.
- **Current and prior systemic medications**: corticosteroid therapy, other medications
- **Allergies or intolerance to medications** (topical or systemic)
- **Family history**: visual loss or blindness due to glaucoma, other ocular disorders

- **Race and ethnicity**: individuals of African or Hispanic origin are at a higher risk to develop POAG, whereas Asian individuals are more susceptible to PACG.
- **Review of notes from previous ophthalmology or optometry visits**: IOP measurements, visual field testing, description of optic discs appearance, fundus photographs, optical coherence tomography (OCT) examinations

Self-reported Visual Function

The patients with glaucoma report the reducing of visual function with impact on their quality of life (QoL). Therefore, specific QoL questionnaires have been developed in order to be used for clinical and research purposes. The glaucoma patients complain the most about the impact of the disease on their psycho-social and driving related activities. These questionnaires help the doctors to become aware about the patients' needs, thus improving communication which is the foundation of improving the compliance to treatment.

Clinical Ophthalmic Examination

Upon examining initially a glaucoma patient, the following tests should be carried on:

- **Best corrected visual acuity** for distance and near for each eye.
- **Testing the pupillary reflexes** may reveal a relative afferent pupillary defect. RGCs represent the initiation site of the light reflex, therefore it may be affected in glaucoma. Since the glaucomatous involvement in asymmetrical, a relative afferent pupillary defect may be identified.
- **Slit-lamp examination of the anterior segment** may show various signs related to glaucoma, such as:
  - shallow AC;
  - pigment dispersion syndrome: Krukenberg spindle, transillumination defects in the mid-periphery of the iris;
  - PEX syndrome: deposits of pseudoexfoliation material on the corneal endothelium, margin of the pupil, anterior lens capsule;
  - inflammation;
  - anterior segment neovascularization.
- **IOP measurement** should be performed in each eye prior to gonioscopy and instillation of mydriatics. Goldmann applanation tonometry (GAT) is gold standard for IOP measurement. Various devices for the self-monitoring of IOP are available (e.g., iCare Home tonometer), but they cannot replace GAT carried on in the clinical setting. It is of utmost importance to document the time of the day when the IOP was measured, taking into account the diurnal variations of the IOP.

- **Gonioscopy** assesses the AC angle opening and may show highly important signs suggesting trabecular dysfunction: pigment accumulation in the TM, new vessels, peripheral anterior synechia. There are various grading systems for the AC angle (e.g., Spaeth Grading System).
- **Fundus examination** is essential in the clinical evaluation of glaucoma patients. Optic nerve head (ONH) is best examined stereoscopically with a magnified view, going through the following protocol:
  - *Optic disc size, shape, and tilting*: The size of the optic disc, as well as the excavation and neuroretinal rim varies within the population, with larger cups being found in larger discs. Any shape anomaly of the optic disc, pits, drusen and tilts must be documented.
  - *Neuroretinal rim (NRR)*: The axons of the RGCs which are supported by the glial cells compose the NRR. Glaucoma is an optic neuropathy defined by the progressive loss of NRR which in contrast with other optic neuropathies is not accompanied by the proliferation of the glial cells, which leads to optic disc cupping. NRR can be lost diffusely, focally (notching) or both. A distinctive feature of glaucomatous optic disc is that the remaining NRR is not pale. Typically, the NRR glaucomatous changes start at the inferior and superior poles of the optic disc.
  - Cup-to-disc ratio (CDR) was described in the 1960s and has been used worldwide as a sign of glaucoma; however, CDR has several shortcomings: first of all, it is measured vertically or horizontally, without considering the size of the optic disc; secondly, CDR does not evaluate the focal NRR loss along other meridians of the optic disc. Asymmetrical CDR with a difference of more than 0.2 between the eyes has been described also in optic neuropathies not related to glaucoma.
  - The Disc Damage Likelihood Scale (DDLS) was elaborated by Spaeth in 2002 and it focuses on the NRR width rather than the extent of the cup, marking the site where the NRR is the thinnest. This scale also adjusts the rim-to-disc ratio to the optic disc size. DDLS turned out to be more accurate and reliable in the diagnosis of glaucoma than CDR, despite its limitations related to discs with atypical rims, such as the tilted ones.
  - *Optic disc vessels*: There are some changes of the optic disc vessels which are typical for glaucoma, such as the nasal displacement of the central ONH vessels, their bending bayoneting and baring of circumlinear vessels.
  - *Optic disc hemorrhages*: The presence of optic disc hemorrhages involving the parapapillary portion of the retinal nerve fiber layer, NRR or lamina cribrosa, signals a higher risk of glaucoma progression.
  - *Retinal nerve fiber layer (RNFL)* In order to assess better the RNFL, red-free filter, low magnification, and focalization slightly anterior to the retinal vessels should be used. In glaucoma, the RNFL can be lost in a localized manner—appearing as a dark band oriented toward the superior-temporal or inferior-temporal disc sector, or diffusely—when it appears as a loss of brightness and density of striations. In early stages of glaucoma, the papillomacular

bundle is typically spared which is why visual acuity and color vision remain normal for long times.

– *Beta-zone parapapillary atrophy* is caused by the atrophy of the retinal pigmented epithelium and of the adjacent choriocapillaris, allowing the large choroidal vessels and sclera to be visualized. Despite its relatively high frequency among glaucoma patients, this sign is not pathognomonic for glaucoma.

Whenever possible, the aspect of the ONH should be documented using stereoscopic or, if unavailable, conventional disc photography.

Diagnostic Testing

- **Visual field evaluation** is the most important test evaluating the visual function in the diagnosis and monitoring of glaucoma. The visual field (VF) must be performed for each eye separately by using static computerized perimetry with standard white-on-white stimuli. The perimeter the most commonly used is the Humphrey Field Analyzer (HFA; Carl Zeiss Meditec, Jena, Germany) which provides standardized algorithms for the testing of the central 24° and 30° of the visual field, where the majority of the RGCs are found.
- When the 24-2 test pattern is used, 54 test points within the central 24°, located 6° apart are analyzed; the test is extended to 30° nasally. The 24-2 test has replaced the 30-2 test in glaucoma because it is shorter and has lower test-retest variability. The 24-2 test has been improved as 24-2C test that evaluates 10 additional points within the central 10°. Another pattern is the 10-2 test which evaluates 68 points located within the 10° central field, located 2° from each other and is indicated for the evaluation of patients with significant VF constriction or having scotomas close to fixation.
- There are various testing strategies: the Swedish Interactive Thresholding Algorithm (SITA) includes SITA Standard, SITA Fast, and SITA Faster.
- If test reliability is low, it must be repeated after reinstructing the patient. It is recommended not to use the first VF as reference, but to consider it as a learning experiment.
- Most VF defects in glaucoma are isolated, but in the advanced stages of the disease, diffuse visual field loss can occur. Glaucomatous VF defects are the subject of specific patterns which represent the translation into function of the anatomic defects respecting the distribution of the retinal nerve fiber layers (RNFL): nasal step, temporal wedge, arcuate and paracentral scotomas, generalized constriction.
- The main quantitative parameters provided by the VF report are mean deviation (MD), pattern standard deviation and VF index. Glaucoma Hemifield Test (GHT) evaluates five predefined areas of the superior hemifield based on the normal

RNFL distribution and compares these areas with the mirrored zones from the inferior hemifield. The GHT message "Outside normal limits" on follow-up examinations is a powerful evidence for glaucoma.

- The MD value issued by the report is important for the staging of glaucoma. Thus, if MD is ≤6 dB, glaucoma is considered early, at MD value between 6 and 12 dB glaucoma is considered moderate and advanced glaucoma is defined by MD >12 dB.
- **The structural assessment of ONH, RNFL and macula** is most commonly performed using OCT devices. The cells affected primarily in glaucoma are the RGCs whose axons form the fibers of the optic nerve and the RNFL.
- Scanning the ONH with OCT evaluates not only the thickness of the circumpapillary RNFL, but also additional areas such as disc, NRR, CDR and cup volume. With the help of enhanced-depth imaging of spectral domain SD-OCT or swept source SS-OCT, the morphology of the LC can be assessed, although this evaluation is not performed routinely in the clinical setting.
- Glaucoma affects not only the circumpapillar RNFL, but also the macular RNFL, the ganglion cell layer (containing the bodies of the RGCs), and the inner plexiform layer (which is formed by the dendrites of the RGCs and the dendrites of bipolar cells, horizontal cells and amacrine cells). The automatic segmentation OCT algorithm of the macular scan is able to measure all of the above mentioned retinal layers, but it must be taken into account that these may vary between different OCT devices. In advanced stages of glaucoma, when circumpapillary RNFL is so profoundly thinned that it is impossible to measure any further loss (so called floor effect), the macular scan is more effective.
- In order to get meaningful results, they must be compared to a normative database, keeping in mind that the measurements obtained with different OCT devices are not interchangeable. Also, the morphological results provided by OCT must be integrated and interpreted along with the data provided by the clinical exam, avoiding the exclusive use of OCT for diagnosing and monitoring glaucoma.
- **Other tests**
  - *Pachymetry*: even if it may be useful for the baseline evaluation of a glaucoma patient, IOP correction according to central corneal thickness is not advisable.
  - The imaging of the AC angle (*anterior-segment OCT*, *Scheimpflug imaging* or *ultrasound biomicroscopy)* offer useful information on the iris and lens, but it cannot replace gonioscopy. They may prove beneficial in patients in which gonioscopy is impossible.
  - *OCT angiography (OCTA)* may show the decrease of retinal vascularization in the peripapillary and macular areas in patients with glaucoma compared to controls, but due to the high variability of testing algorithms and parameters between different OCTA instruments, there is no consensus of standard OCTA evaluation (Mannil et al. 2023).
  - *Microperimetry* is not routinely indicated in glaucoma patients, proving its benefits in situations where there is localized RNFL loss and normal HFA tests.

- *Electrophysiological tests* do not replace VF examination.
- *The deep learning system of artificial intelligence* can assist ophthalmologists to identify aspects that are typical for glaucoma on fundus photographies, VF and OCT.

Diagnosis

Diagnostic Strategy

Integrating all the information provided by the clinical evaluation and the examinations presented above, the following algorithm for managing the patient with glaucoma is proposed:

- **If the VF is**:
  - *Normal*:

    If there is *no structural abnormality*, the patient does not have glaucoma.
    If *structural abnormality* was identified, causes of optic nerve anomalies other than glaucoma should be ruled out.

  - *Borderline*:

    In case of *no structural abnormality*, it is recommended that the patient be retested and to rule out other optic neuropathies.
    In case of *corresponding structural abnormality*, the diagnosis of glaucoma is confirmed.

  - *Definitely abnormal*

    If *no structural abnormality* was identified, the VF examination must be repeated with a careful check of the reliability indices; if the VF is still abnormal, other causes of impairment of the visual function must be sought.
    If *corresponding structural abnormality* was identified, the diagnosis of glaucoma is confirmed.**Important: even though elevated IOP is a major risk factor for glaucoma, its value is not part of the glaucoma diagnostic algorithm.**

Differential Diagnosis

Before affirming the diagnosis of glaucoma, conditions that evolve with abnormalities of the optic disc and changes in the VF must be eliminated:

- Optic disc abnormalities: congenital (e.g., coloboma, pit), tilted optic discs, dominant optic atrophy, other optic neuropathies after the acute phase (e.g., ischemic, toxic or nutritional, inflammatory)

- Retinal diseases altering the RNFL and the VF: scars following panretinal laser photocoagulation, arterial and venous occlusions, colobomas
- Diseases of the central nervous system: compressive optic neuropathies, disorders of the intracranial visual pathways

Types of Glaucoma

Primary Open Angle Glaucoma

Definition

POAG is a chronic, progressive and irreversible optic neuropathy in adults, characterized by the loss of NRR and RNFL leading to VF defects. Gonioscopy reveals a normal and open angle of the AC. POAG is always bilateral, but often asymmetric.

Etiology and Mechanism

The precise cause of POAG is yet unknown. It is believed that several genetic factors associated with various co-morbidities may be involved in the pathogenesis of POAG. An imbalance between IOP levels and individual tolerability seems to be the cause of LC distortion resulting in the damage of the optic nerve axons and apoptosis of the RGCs. The increase of the IOP values is produced by the elevated outflow resistance within the TM.

POAG Suspect

When the results of the structural and/or functional assessment of a person are at borderline, the glaucoma suspect is defined. One such example is represented by normal or increased IOP associated with at least one of the next features being suspicious: optic disc and/or RNFL, and/or VF normal or suspicious.

Ocular hypertension (OHT) is a notion that includes patients with IOP >21 mmHg without treatment and with all structural and functional parameters within the normal range (VF, AC angle, optic disc, RNFL) and no history of steroid treatment or ocular disease.

Diagnosis of POAG

History

- Black and Latino races are at higher risk for developing POAG.
- Family history may identify first degree relatives with confirmed POAG.
- It is important to identify conditions associated with the risk of POAG: diabetes, migraine headache, systemic hypertension, Raynaud's syndrome. It is also significant to be aware of any disease that could interfere with the glaucoma medication, especially with the beta-blockers, like asthma, chronic obstructive pulmonary disease, cardiac failure.
- The use of steroids can modify IOP values.
- In the ocular history, refractive errors, prior ocular surgery, trauma may be significant for the association with glaucoma.

Ophthalmological Clinical Examination

1. *Slit-lamp anterior segment examination* must identify any feature relevant for a secondary mechanism of glaucoma, such as:
   (a) cornea: exfoliation material, Krukenberg spindle
   (b) anterior chamber depth
   (c) iris: transillumination defects, neovascularization
   (d) lens: exfoliation material
   (e) inflammation
2. *IOP measurement*: the gold standard is Goldman applanation tonometry that should be performed before gonioscopy and pupil dilation.
3. *Gonioscopy*: the Spaeth gonioscopy grading system allows to describe the AC angle anatomy and to assess its depth. Secondary causes of IOP elevation must be ruled out: pigment dispersion, pseudoexfoliation material, PAS or angle neovascularization.
4. *ONH and RNFL clinical examination* identifies glaucomatous optic neuropathy on the ground of its specific features:
   (a) NRR displays either focal narrowing or notching, especially at the superior and/or inferior poles, or diffuse narrowing.
   (b) Optic disc vessels are decentered nasally.
   (c) The circumlinear vessels are bared.
   (d) Striate haemorrhages can be visible on the optic disc at the level of the NRR, in the parapapillar region of the RNFL or LC.

(e) Increased cup/disc (C/D) ratio is the consequence of the progressive narrowing of the NRR.
(f) The remaining NRR is not pale, but it keeps its normal colour.
(g) There can be identified the focal or diffuse thinning of the parapapillar RNFL, especially at the inferior or superior poles.
(h) The atrophy of the parapapillar beta-zone, although present in many cases of glaucoma, is not a specific sign.

Diagnostic Testing

1. *CCT measurement* CCT below 555 μm is associated with a higher risk of developing POAG. However, there is no generally accepted correction formula for the IOP value depending on CCT.
2. *Visual field evaluation* The VF damages consistent with RNFL thinning are: nasal step, arcuate scotoma, paracentral depression in clusters of test sites. In early/moderate cases, the loss of VF across the horizontal midline in one hemifield that exceeds loss in the opposite hemifield is very suggestive for the diagnosis of glaucoma.
3. *ONH, RNFL and macular imaging* must always be integrated with the results of the clinical examination of the glaucoma patient. The most important structural alterations consist in the thinning of the parapapillary and macular RNFL.

Management

The goal of treatment in glaucoma patients is to stabilize the disease progression, meaning to reach a target IOP at which the VF, optic disc and RNFL are stable.

Thus, each glaucoma patient has its own target IOP. In setting the goals, various factors should be taken into account in defining the target IOP. For instance, younger patients require lower target IOP and so do the ones with faster progression rates. The lower the untreated IOP, the lower the target IOP must be. The more advanced the glaucoma and the more severe the structural and functional deficits, the lower the target IOP must be.

The Choice of the Method to Lower IOP

Medical Treatment

Start with Monotherapy

With the exception of very advanced and severe cases, the treatment of a glaucoma patient starts with monotherapy. The drugs that lower the IOP the most are the prostaglandin analogues (PGAs), followed by non-selective beta-blockers, Rho kinase

inhibitors, alpha-adrenergic agonists, selective beta-blockers and at last, topical carbonic anhydrase inhibitors (CAI).

Switch to Another Monotherapy

If the initially prescribed drug is ineffective or intolerable, it is changed to another one from the same class or from a different class. Combination therapy is not recommended initially, unless the glaucoma is very severe or in an advanced stage.

Laser trabeculoplasty is another option.

Add a Second Drug or Use a Combination Therapy

If the initial monotherapy is well tolerated, but the target IOP is not reached, a drug from a different class is added. Because the multiple instillations of drugs can reduce adherence to treatment and increase the risk of exposure to preservatives, it is preferable to indicate fixed drug combinations instead of separate instillations of drugs. If two drugs are insufficient to reach the target IOP, either a third agent is added, or laser or incisional surgery should be considered.

Laser Therapy

Laser trabeculoplasty is indicated either initially, or as a replacement or add-on treatment. Initially it is effective in 80–85% of cases, producing a 20–25% IOP reduction, but the effect diminishes over time, requiring the treatment to be repeated. Fortunately, it is a repeatable procedure.

Incisional Surgery

Penetrating Glaucoma Surgery: Trabeculectomy

Trabeculectomy is indicated in the following patients with POAG:

(a) If drug or laser treatment failed to control the disease or is not suitable due to side-effects or non-compliance.
(b) In patients with high IOP at presentation or advanced glaucoma in which the target IOP is unlikely to be reached with medication or laser.

The non-penetrating glaucoma surgery techniques (deep sclerectomy, canaloplasty or viscocanalostomy) are indicated in low risk POAG.

The insertion of glaucoma drainage devices (Molteno, Baerveldt, Ahmed) is indicated in patients who are likely to have poor results if trabeculectomy with antifibrotic agents is carried out.

Minimally Invasive Glaucoma Surgery (MIGS) is indicated in mild to moderate forms of glaucoma, because the IOP-lowering effect is modest.

Normal tension glaucoma (NTG) is a variant of POAG in which IOP is normal during the diurnal testing. In the pathogenesis of NTG, factors that increase the vulnerability of the optic disc play the major role, such as vascular dysregulation, arterial hypotension abnormalities of LC. There are some clinical features that individualize NTG within the group of patients with POAG: CCT is lower and lower IOP is more prevalent in women with vascular dysregulation (headache migraine, Raynaud's syndrome). Also there are some specific features at the level of the optic disc that are noted more frequently in NTG: flamed shaped disc haemorrhages, peripapillary atrophy, focal and deep notching of the NRR. Regarding the modifications of the VF, paracentral scotomas occur more frequently in NTG.

Different types of optic neuropathies (ischemic, inflammatory, compressive, toxic, traumatic, congenital) could be mistaken as NTG.

Before initiating treatment in NTG, progression should be proved, since 50% of untreated patients will be stable at 5–7 years.

Medical treatment includes PG as initial therapy, brimonidine due to its neuroprotective additional effect. Topical beta-blockers should be administered with caution due to the known significant dip in the blood pressure over night related to their use with subsequent decrease of the perfusion pressure and increasing vulnerability at the optic nerve head. If progression occurs even if IOP is in the low teens, surgery is indicated. In order to counteract vasospasm, systemic calcium-channel blockers are prescribed.

Primary Angle Closure Glaucoma

Definition and Classification

There are several terms defining various scenarios related to primary angle closure glaucoma.

A primary angle-closure suspect (PACS) is defined by normal IOP and no optic disc nerve damage, but iridotrabecular contact (ITC) on ≥180 degrees.

Primary angle closure (PAC) includes elevated IOP, no optic disc nerve damage, ITC ≥180 degrees and peripheral anterior synechiae (PAS).

Primary angle-closure glaucoma (PACG) adds the optic neuropathy to the features defining PAC.

Acute angle-closure crisis (AACC) or Acute primary angle closure (APAC) with the previous name of "acute glaucoma" refers to an occluded angle with symptoms and acute elevated IOP.

Causes and Pathogenesis

The predisposing risk factors are constitutional: high hyperopia, shallow AC and angle, bulky lens. They can be summarized by the phrase: "voluminous lens in small eye".

Triggering risk factors are represented by the conditions that favor the installation of mydriasis: stress, obscurity, instillations of mydriatics.

Pathogenesis

The cause of the glaucoma attack is pupillary blockage. The steps leading to angle closure and its consequences are:

- Normally, at the level of the pupil there is a physiological pupillary block which causes the AH circulation to occur more slowly at this level.
- In the previously stated conditions, the pupillary block increases, becoming pathological, so that the AH can no longer pass through the pupil.
- AH accumulates in the posterior chamber, pushes the iris root anteriorly and it closes the angle, making it impossible for AH to access the TM.
- The AH can no longer evacuate, which leads to a marked increase in IOP, with the following consequences:
  - alteration of the corneal endothelium → edema;
  - ischemia of the iris sphincter muscle → fixed semi-mydriasis;
  - optic atrophy → definitive decrease in VA.

Diagnosis

History

- In the patient's history, symptoms of intermittent angle closure, either spontaneous, or following the administration of mydriatic eye drops or oral anticholinergics, can be found: headache, blurred vision, coloured halos around light, eye redness and pain.
- There are drugs responsible for angle closure: sulfonamide (which produce ciliary body edema with subsequent narrowing of the angle) or phenothiazines, salbutamol and ipatropium bromide (with adrenergic or anticholinergic effect).
- There can be family history of AACC.

Ophthalmological Examination

1. *VA* is decreased in AACC.
2. *Refraction*: most patients with PACG are hyperopic.
3. *The pupil*: During or following an AACC, the pupil is mid-dilated, vertically oval, asymmetric and with a poor or absent response to light.
4. *Slit-lamp biomicroscopy* in AACC displays the following signs:
   (a) the eye is red with conjunctival perilimbal injection;
   (b) the AC is shallow centrally and peripherally and with flare;

(c) there are microcysts and stromal edema at the level of the cornea;
(d) the iris shows focal or diffuse atrophy, as well as posterior synechiae;
(e) "glaukomflecken" is a term describing specific opacities of the lens located under the anterior capsule with the shape of patches.

5. *IOP* is very high (50–80 mmHg) during AACC, low, following intensive treatment or ciliary body shutdown, or intermittently elevated in chronic presentation.
6. *Gonioscopy* is difficult during AACC due to corneal edema. In order to differentiate between appositional and permanent angle closure, indentation gonioscopy should be performed.
7. *Fundus and optic nerve head evaluation*. In AACC that was resolved immediately, optic nerve congestion and choroidal folds are seen, while if it was resolved with delay, the optic nerve can be normal, pale and/or cupped.

Diagnostic Testing

1. *Anterior segment imaging*. Anterior segment OCT (AS-OCT) reveals the opening depth of the AC angle, the area between the iris and TM and the angle recess area, but it has minor contribution in imaging the anomalies of the ciliary body and the posterior aspect of the iris. These latter structures as well as the plateau iris configuration are better described with ultrasound biomicroscopy (UBM).
2. *Ocular biometry* determines the axial length and intraocular lens power.

The goals of the management are to reverse or prevent angle-closure process, control the IOP and prevent the damage to the optic nerve.

PACS

- **Laser iridotomy (Nd:YAG LPI)** is indicated in eyes with high risk for angle closure, that is those with very high hyperopia, positive family history and concomitent retinal disease that requires pupil dilation.
- If following laser iridotomy the ITC persists, one of the following attitudes is chosen: observation, thermal laser peripheral iridoplasty (TLPI) or lens extraction.

AACC

The emergency treatment aims three goals: to reduce AH production, to constrict the pupil and to reduce inflammation.

- *Reduction of AH production* is made with Acetazolamide, according to the IOP value. Thus, if IOP is lower than 50 mmHg, it is administered orally, whereas if

IOP is equal to or above 50 mmHg, it is administered intravenously, 10 mg/kg. The systemic treatment is supplemented with the topical one: apraclonidine 0.5% or 1% and timolol 0.5% at 5 min interval.
- *Pupillary constriction* is initiated only after the IOP has been lowered and it is achieved with Pilocarpine 1% or 2% one drop with a second dose after half an hour.
- *In order to reduce inflammation*, topical steroid prednisolone 1% or dexamethasone

0.1% every 5 min for three times then 4–6 times/day are given.

Other therapeutic actions
- In case of corneal epithelial edema, visualization can be improved with topical 50% glycerol.
- To dehydrate the vitreous body, several options are available: Mannitol 20% 1.0–2.0 g/kg IV over 30 min–1 h or oral glycerol 50% 1.0–1.5 g/kg or oral isosorbide 1.0–1.5g/kg.

Curative Treatment Once the cornea is clear, Nd-YAG peripheral iridotomy has to be carried out. In case it is or possible or available, surgical iridectomy should be performed. If the IOP remains elevated following the attack and the angle is still closed after LPI, lens extraction is recommended. Trabeculectomy is indicated in the cases with persistent elevated IOP despite successful LPI.

PAC and PACG

- **LPI with the Nd-Yag laser** is less effective in PACG with extensive PAS >180 degrees and advanced optic nerve damage.
- **Medical treatment** is indicated if despite the opening of the AC angle the IOP continues to be elevated or if there is substantial synechial angle closure.
- **Phacoemulsification with intraocular lens implantation** by deepening the AC opens the angle. It has been proved that clear lens extraction was superior to standard LPI regarding IOP control and QoL in patients with PAC with IOP above 29 mmHg or PACG.
- If PACG is advanced or uncontrolled, early **Lens extraction** or **Trabeculectomy with mitomycin C** or combined surgery should be performed.

Secondary Glaucomas

Whenever the cause of elevated IOP leading to optic nerve damage and vision loss can be identified, the glaucoma is considered secondary. It can be classified according to the opening of the angle, as open or closed angle. The causes of secondary glaucomas are varied: lens-induced, inflammatory, pigmentary, pseudoexfoliating, neovascular, hemorrhagic, steroid induced, traumatic.

Lens-induced glaucomas can be closed or open angle.

Closed angle lens-induced glaucomas can be phacomorphic, when produced by an intumescent lens, or phacotopic, caused by anterior subluxation or dislocation of the lens and spherophakia.

Regardless of the circumstance, the lens pushes the iris forward and closes the angle. This is translated into the clinical picture as *n* acute congestive glaucoma with the features of an APAC glaucoma. Lens extraction and IOL implantation must be performed immediately after reducing the IOP with medical treatment: mannitol intravenously, systemic acetazolamide and topical beta-blockers +/− CAI.

Open angle lens-induced glaucomas can be: phacolytic, lens particle or phacoantigenic.

1. *Phacolytic glaucoma* is a complication of hypermature cataract, being caused by the clogging of the TM with lens proteins, macrophages phagocitosing the lens proteins and inflammatory debris. The symptoms appear suddenly usually in older individuals with long time decreased vision and consist in ocular pain, congestion and watering. The eye is red, but the AC is deep and in the AH, protein deposits as pseudohypopyon can be identified. The treatment consists in the extraction of the lens and its replacement with an IOL, after lowering the IOP and treating the inflammation with medical means.
2. *Lens particle glaucoma* occurs after trauma or surgery being caused by lens fragments that block the TM. The symptoms are of acute hypertensive uveitis associated with the presence of lens fragments in the AC. The treatment consists in the surgical removal of the lens fragments associated with IOP lowering and anti-inflammatory eye drops.
3. *Phacoantigenic (phacoanaphylactic) glaucoma* is the consequence of a sensitization mechanism to the own patient's lens proteins through an antigen-antibody reaction that appears clinically as a fulminating inflammatory reaction. The first event is the disruption of lens capsule and it is followed by the leak of lens proteins which are non-self and initiate an autoimmune reaction manifesting as a granulomatous inflammation of the uvea with elevated IOP. Treatment consists in the removal of the lens and associated medical therapy aiming the IOP lowering and resolving of inflammation.

Inflammatory glaucomas can be open or closed angle.

Open angle inflammatory glaucoma can be acute or chronic.

- In acute open angle inflammatory glaucoma, there is edema and clogging of the TM. It manifests as iridocyclitis with raised IOP and open AC angle.
- In chronic open angle inflammatory glaucoma, the elevation of IOP is caused by chronic trabeculitis and trabecular scarring. Management includes medical therapy, incisional surgery (trabeculectomy), cyclodestructive procedures.

Angle Closure Inflammatory Glaucoma

The pupil can be blocked or not. If the pupil is not blocked, the cause of angle closure is represented by the anterior synechiae. IOP is elevated, AC is shallow. In order to prevent this condition, prompt and intensive treatment of uveal inflammation should be done. Once glaucoma appears, its treatment includes medical therapy, laser iridotomy and filtration surgery.

Inflammatory Ocular Hypertension Syndrome (IOHS) is the consequence of the direct inflammation of the TM. Its most frequent causes are herpetic anterior uveitis and Postner-Schlossman Syndrome (PSS). Other less common etiologies are sarcoidosis, toxoplasmosis, listeriosis, cytomegalovirus disease and syphilis.

- PSS or glaucomatocyclitic crisis affects young adults, aged between 20–50 years and manifests clinically as acute, unilateral increase of IOP accompanied by mild AC reaction or fine white corneal precipitates. The vision is slightly blurred, lasting from several hours to weeks. Between the attacks, there is no sign of inflammation and IOP is normal. The VF and optic disc are normal. The pathogenesis of PSS is not fully understood. Treatment consists in lowering IOP and controlling inflammation.

Uveitis-Glaucoma-Hyphema Syndrome (UGH) results from the friction between an IOL (especially anterior chamber) and the iris. As a consequence of this friction, there will be transillumination defects, dispersion of pigment and hyphema with subsequent elevation of IOP. Over time, chronic inflammation develops with cystoid macular edema (CME), rubeosis iridis and recurrent hyphemas. The incidence of UGH syndrome has decreased significantly as consequence of the improvements in IOL technology and surgical techniques.

Pigmentary glaucoma typically affects males with myopia, aged between 20–45 years and is caused by the release of pigment from the iris and its storage in the TM. The pigment is also deposited in the cornea, lens and other parts of the eye. Not all individuals with pigment dispersion syndrome develop glaucoma. The mechanical rubbing between the posterior pigmented layer of the iris and the zonular fibers causes the release of pigment. The clinical features are similar with POAG, but there are some signs that are specific for pigmentary glaucoma: the iris is concave and at transillumination, radial slit-like defects in the iris periphery are revealed, the AC is deep and gonioscopy shows the Sampaolesi's line which is pigment accumulation along Schwalbe's line, especially inferiorly. The pigment is also deposited in the cornea, under the shape of Krukenberg's spindle and on the lens, as Sheie's line/Zentmayer's ring. Pigmentary glaucoma responds to laser trabeculoplasty better than POAG.

Pseudoexfoliation glaucoma (PEX) is caused by an amorphous grey, dandruff-like material which is deposited within the drainage system of the AH, thus causing the elevation of the IOP and optic nerve damage. It is It occurs more frequently in women, Scandinavians and the connection with a mutation in LOXL1 gene at 15q22 locus has been demonstrated.

Pathogenesis: the TM is clogged with PXF material and irian pigment. The PXF material is made up of a protein core which is surrounded by GAGs originating in the basement membranes of the aged epithelial cells within the TM, lens capsule and ciliary body.

Clinical picture: the objective examination of the eye provides specific signs for PEX. On the corneal endothelium there is dandruff like material; at gonioscopy, Sampaolesi's line is identified; the pupillary margin of the iris has a moth-eaten aspect and transillumination defects at the iris are visible; the lens presents cataract, with the exfoliative material disposed in a typical manner under the shape of a central disc with a peripheral band and a clear zone between them.

The treatment follows the same guidelines as POAG, but it responds better to laser trabeculoplasty. In order to prevent the rubbing of the papillary margin of the iris against the lens with subsequent release of exfoliative material, miotics are indicated.

Glaucoma Secondary to Intraocular Hemorrhage

- *Red cell glaucoma* appears in recent massive hyphema, being caused by the red blood cells (RBC) that block the TM.
- *In haemolytic glaucoma*, the TM becomes clogged with macrophages that are loaded with debris from the RBCs.
- *Ghost cell glaucoma* is a complication of vitreous hemorrhage in the aphakic or pseudophakic eyes. At the clinical examination, in the vitreous can be identified the Heinz bodies which are degenerated RBCs. They are named ghost cells, due to their appearance as tan-colored empty spheres.
- *In hemosiderotic glaucoma* the TM becomes sclerozed by the iron originating in the phagocytised hemoglobin.

Neovascular glaucoma (NVG) results from the formation of a neovascular membrane involving the anterior chamber angle. Iris neovascularization is the consequence of retinal diseases having in common retinal ischemia.

Neovascular glaucoma has various causes:

- Ocular vascular diseases: proliferative diabetic retinopathy, central retinal vein occlusion, anterior segment ischemia, sickle cell disease, Coat's disease, Eale's disease, retinopathy of prematurity, radiation therapy, persistence of the hyperplastic vitreous.
- Systemic vascular diseases: carotid occlusive disease, carotidocavernous fistula, giant cell arteritis, Takayasu arteritis.
- Intraocular tumors
- Trauma: accidental, open globe surgeries in patients with diabetes mellitus
- Other: chronic uveitis, chronic retinal detachment, endophthalmitis, Stickler syndrome, retinoschisis

In the evolution of NVG, four stages were defined:

- Pre-glaucoma: new vessels appear at pupillary margin of the iris and in the angle
- Open-angle glaucoma: new vessels expand and a fibrovascular membrane lines the angle
- Secondary angle closure glaucoma: the heavy neovascularization and extensive peripheral anterior synechiae close de angle
- Regression: the angle is sealed, which is why the new vessels are less visible.

Treatment aims to decrease the IOP (betablockers, CAI, acetazolamide), resolve the inflammation (topical steroids and mydriatics) and address the retinal cause (panretinal photocoagulation, anti-VEGF injections). Medical treatment alone is usually not able to lower efficiently the IOP. Artificial filtration shunts are indicated. Cyclodestructive procedures and retrobulbar alcohol injections are palliative means aiming to relieve pain.

Glaucoma Associated with Iridocorneal Endothelial (ICE) Syndromes

This entity includes three conditions:

- Progressive iris atrophy
- Chandler's syndrome
- Cogan-Reese syndrome

The common denominator of these three conditions is represented by the presence of abnormal corneal endothelial cells which proliferate forming an endothelial membrane that lines the anterior chamber angle, thus preventing the AH to reach the drainage system.

Typically, glaucoma associated with ICE syndromes occurs in middle-aged women. There are differences between the three conditions based on which they are individualized:

- In progressive iris atrophy, iris features are predominant, consisting in corectopia, iris atrophy and the formation of holes.
- In Chandler's syndrome, corneal edema is predominant, whereas iris features are mild.
- In Cogan-Reese syndrome, nodular and diffuse pigmented lesions are seen on the iris and corneal changes are associated or not.

Treatment includes medical therapy, trabeculectomy and filtration devices.

Steroid-induced glaucoma occurs most frequently following ocular administration of steroids (drops, ointments, intraocular or peribulbar injections), but also after their regional use on the skin around the eye, or systemic administration (oral, inhaled, intravenous). There is an increased risk for patients with POAG to develop steroid induced intraocular hypertension or glaucoma. The treatment of steroid-induced glaucoma is similar to POAG, along with steroid discontinuation, if possible.

Traumatic Glaucoma

Pathogenesis

There are varied mechanisms explaining the occurrence of traumatic glaucoma: inflammation, intraocular hemorrhage, lens-induced, fibro-epithelial ingrowth, angle-recession, chemical burns with subsequent shrinkage of the sclera and disrupting the architecture of the drainage pathways of the AH. Electric trauma can lead to transient IOP increase by several mechanisms: venous dilatation, extraocular muscle contraction and pigment dispersion. Radiation can also be at the origin of glaucoma, by retinopathy and vitreous hemorrhage which can lead to neovascularization and ghost cells.

Glaucoma in aphakia occurs early postoperatively with elevated IOP and deep AC. The mechanisms involved in its pathogenesis are varied: closure of the angle due to a flat AC or pupillary block, pre-existing missed POAG, steroids, epithelial ingrowth, malignant glaucoma.

In the glaucoma associated with intraocular tumors IOP can become elevated as consequence of the trabecular blockage by tumor cells, angle neovascularization, venous stasis, forward displacement of the iris-lens diaphragm with the closure of the angle. The eye should be enucleated.

Cilliary block glaucoma is a rare disease that can complicate any intraocular surgery. The surgery associated with the highest risk of cilliary block glaucoma is peripheral iridectomy or trabeculectomy performed in patients with PACG. The patient is in severe pain and complains of blurred vision after surgery. IOP is elevated and the AC is shallow or absent, there is no response or even aggravation after miotics. The patient can be phakic, pseudophakic or aphakic. Treatment consists in medical therapy (1% atropine drops, acetazolamide, topical beta-blocker, iv mannitol), YAG laser hyaloidotomy, surgical therapy.

Childhood Glaucoma

Fortunately, childhood glaucoma is a relatively uncommon condition, because IOP control is very challenging with devastating consequences on the visual function.

Primary Childhood Glaucoma (PCG)

Childhood Glaucoma Research Network defines PCG as being characterized by an immature angle with trabecular dysgenesis and classifies it based on the age at onset, as follows:

1. **Neonatal-onset glaucoma or glaucoma presenting at less than 1 month old** includes any developmental anomaly that causes glaucoma at birth. Since the

developmental pattern occurs in utero, the development of the AC is arrested early and the disease is more severe. Because of the high IOP in utero, the new born has cloudy and enlarged corneas (megalocorneas). The prognosis is poor, with unfavourable surgical and functional results.

2. **Infantile glaucoma (1–24 months)** manifests with the triad: epiphora, blepharospam and photofobia. In most instances (70% of cases), the disease is bilateral, although sometimes asymmetric. As result of the chronically elevated IOP, the eye which is elastic at this age, becomes enlarged (buphthalmia or ox eye) and the cornea is usually cloudy.
3. **Late onset or late recognition (>24 months)**
4. **Spontaneously arrested (nonprogressive buphthalmous)** presents with Haab's striae and normal IOP and optic nerves.

In juvenile open-angle glaucoma the angle is open and normal. It occurs late in childhood, between 3 and 40 years of age. IOP is significantly elevated, but there is no buphthalmia, as the debut is later, when the eye is less elastic. No other ocular anomalies or systemic features were identified, but in most instances there is a strong family history of glaucoma with autosomal dominant inheritance.

Secondary Childhood Glaucoma

Glaucoma associated with nonacquired ocular anomalies includes conditions that manifest at birth, predominantly at the eye level, with or without systemic signs.

- Although aniridia means the absence of iris, in this condition there is always a periferal iris remnant that progressively closes the angle. It is a bilateral disease, extremely variable, in which PAX6 gene mutations at chromosome 11p13 were identified. Inheritance is most frequently autosomal dominant with high penetrance and variable expressivity, but it can also be sporadic. Aniridia can be associated with WARG syndrome (Wilms tumor, Aniridia, Genitourinary anomalies and intellectual disability) in 30% of cases. In more than 50% of cases glaucoma occurs in preadolescence or early adulthood.
- Axenfeld-Rieger anomaly (or syndrome if there are systemic associations) refers to a spectrum of overlapping clinical features including posterior embryotoxon (proeminent Schwalbe's line) with attached iris strands and iris anomalies (corectopia, iris hypoplasia). Systemic anomalies, such as hypertelorism, dental and cardiac abnormalities and periumbilical skin tags, can be present. The inheritance is autosomal dominant with bilateral and asymmetrical presentation.
- Peters anomaly (or syndrome if there are systemic associations) is characterized by congenital corneal opacities localized within the stroma, Descemet's membrane and endothelium. The corneal defect is central and can be isolated or associated with iris and lens involvement. Peters plus is the name of the association with systemic features and carries a higher risk of glaucoma. IOP is often unstable and the onset of glaucoma occurs in childhood or young adulthood.

Other anomalies that can cause glaucoma are: congenital ectropion uveae, congenital iris hypoplasia, persistent fetal vasculature (if glaucoma is present before cataract surgery), oculodermal melanocytosis (nevus of OTA), microphthalmos/microcornea.

Glaucoma Associated with Nonacquired Systemic Diseases or Syndromes

- Sturge-Weber syndrome (encephalotrigeminal angiomatosis) is the most common phakomatosis associated with glaucoma. There is a sporadic facial vascular malformation (port wine stain) and ocular vascular anomalies (episcleral and choroidal haemangioma). Around 30–50% of cases can develop glaucoma from birth to adulthood. The pathogenesis of glaucoma lies in the elevated episcleral venous pressure and goniodysgenesis.
- Klippel-Trenaunay-Weber syndrome is characterized by the association of cutaneous vascular malformations and vascular anomalies involving one limb associated with the hypertrophy of bone and soft tissue.
- Neurofibromatosis is an autosomal dominant disease that may display iris malformations upon presentation, such as ectropion uveae and glaucoma that forego the systemic signs.
- Connective tissue and metabolic disorders such as Marfan's syndrome, Weil Marchesani syndrome and homocystinuria are well known causes of lens dislocation that lead to glaucoma by pupil block and angle closure. Glaucoma can be prevented by iridectomy and chronic miosis.

Glaucoma Associated with Acquired Conditions

- Any cause of inflammation can lead to glaucoma, but the most common condition is juvenile idiopathic arthritis (30%), usually within 2–3 years from presentation. A plethora of factors intervene in the pathogenesis of glaucoma: chronic trabecular obstruction, trabeculitis, peripheral anterior synechiae, posterior synechiae with pupillary block, lensectomy-associated complications, administration of steroids. Glaucoma progresses more rapidly than in adults.
- Blunt or penetrating trauma can lead to acute or chronic rise in IOP that can occur many years after the injury. The pathogenesis of traumatic glaucoma is multifactorial due to angle recession (especially if over 180°), topical steroids or hyphema.
- More uncommon, childhood malignancies, such as leukemia, retinoblastoma or medulloepithelioma, may impend AH outflow by tumor cells or secondary hemorrhage. The most important component of treatment is to address the primary disease.

Glaucoma Following Cataract Surgery

Previously named aphakic and/or pseudophakic glaucoma is one of the most common secondary glaucomas during childhood. Several mechanisms are proposed: **(1) chemical,** according to which glaucoma is the consequence of the inflammatory mediators diffusing from the vitreous or lens into the AC, causing the inflammation and dysfunction of the TM; **(2) mechanical,** postulating as cause of glaucoma, the lack of ciliary body tension and TM collapse; and **(3) developmental issues**. Usually, the angle is open, but PAS may be occasionally present. Angle closure is also possible through an extreme postoperative inflammatory response. The younger the child (especially in those less than 4 weeks of age at the moment of surgery), the greater is the risk of glaucoma. A corneal diameter $\leq$10 mm increases the risk of glaucoma by 3 folds. Other risk factors for the occurrence of glaucoma following cataract surgery in children are the need for a secondary surgery and the nuclear cataract. It is highly important to follow the patient after cataract surgery regarding the risk of glaucoma. Contact lens intolerance or excessive loss of hyperopia are alarm signals in this regard. The management of this type of glaucoma is more difficult and the prognosis is more reserved as compared to PCG.

Management of Childhood Glaucoma

Assessment

Whenever suspected with glaucoma, a child must be seen as soon as possible by a paediatric ophthalmologist. History of photophobia, epiphora, blepharospasm or any change in the appearance of the eye, are important clues for the diagnosis. The age of onset is important, as younger the child at diagnosis, worse is the prognosis. The anaesthetic risk should be evaluated, especially in circumstances in which systemic problems are associated. Family history of childhood glaucoma and parental consanguinity are crucial aspects to clarify.

Tonometry

Applanation tonometry is the gold standard for measuring IOP. The normal IOP values in newborns are lower than in adults and they may be influenced by varied factors: anesthesia, compliance, corneal characteristics.

The Measurement of the Corneal Diameter

In newborns the horizontal corneal diameter is around 10.5 mm and it increases by 1 mm during the first year of life. It is considered that an increase in corneal diameter over 11 mm in a newborn and 12 mm in an infant indirectly certifies the elevated IOP. Haab's striae are very valuable for the positive diagnosis.

Central Corneal Thickness

It is not precisely known in what extent the central corneal thickness influences the IOP value in children. In children with PCG and JOAG the corneas are thinner, as opposed to patients with aphakia and aniridia in who have increased corneal thickness.

Anterior Segment Examination

At the corneal level, there can be oedema, opacities, posterior embryotoxon and Haab's striae. If the corneal oedema is persistent, it can signal a chronic and poorly controlled glaucoma. Portable slit-lamp offers the best way to examine in detail the cornea in infants.

Gonioscopy is crucial for establishing the right diagnosis and the most appropriate treatment and it is recommended to be performed at least once.

Posterior Segment Examination

The most important and reliable parameter to establish the diagnosis and monitor its progression is the aspect of the optic disc. Disc cupping in Caucasian newborns should not exceed 0.3 and 0.2 in terms of asymmetry. Unlike the adults, disc cupping can be reversal in infants following IOP reduction if it occurs prior to irreversible nerve atrophy.

Refraction

The evaluation of refraction can be helpful for diagnosis and follow up of glaucoma. The presence of myopia in a newborn or a significant loss of hyperopia are alarm signs for glaucoma. If an aphakic eye in which myopia progresses, especially if axial length increases progressively, witness the inappropriate IOP control.

Examination Under Anaesthesia

All anaesthetics lower the IOP, excepting ketamine and chloral hydrate. It is recommended to use the same agent with the same approach for the serial measurements of IOP. Also, IOP measurement must be the first manoeuvre in the examination protocol during anesthesia.

Investigations

Measuring the axial length is helpful in diagnosing and monitoring glaucoma. Ultrasound is useful to diagnose conditions like tumours or choroidal hemagiomas that lead to secondary glaucoma. VF can be done around the age of 7–8 years.

Treatment

Medical therapy is an important part of the management. It can be first-line treatment for most glaucomas and often it is necessary to augment the surgical result.

Betablockers are not recommended in premature or newborn infants and in children with cardiac problems or asthma. If not within these categories, Timolol eyedrops 0.1% or gel 0.25% are the beta-blockers in the first line choice. The first prostaglandin agent approved for use in children is latanoprost and is very effective in JOAG patients.

Surgical Therapy

The choice of a certain surgical technique depends on multiple factors, such as the age, stage of the disease, appearance of the cornea, concomitant ocular diseases, any previous surgery and surgeon's preference.

- *Angle surgery* has the best results in PCG and consists in goniotomy combined with trabeculotomy or trabeculectomy.
- *Glaucoma Drainage Devices* are indicated in children with refractory glaucoma, as well as in glaucoma following cataract surgery, situation in which they represent the primary indication.

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Chapter 11
Ophthalmological Pathology and Management in Eye Diseases: Uvea

Marieta Dumitrache

Abstract **Uveitis anterior** (acute, chronic), **intermediate uveitis** (planeed pars), **posterior uveitis**—are an inflammation of the iris, cyliary, body, choroid. Treatment of uveitis is difficult, and often is a treatment symptomatic topic and parabulbar with mydriatic, cycloplegic, NSAID corticoid, as need systemic with corticoid, antibiotic, immunosuppresants (methotrexat, azatioprin, cyclosporin). **Endophtalmidis** are eye disease, affecting ocular contens, aqneous humor and vitreous body, purulent inflammation produced by exogenous infection, endogenous or metastatic. Treatment bacterial of endophtalmidis is emergency with antibiotic topic, intravitreal, systemic, vitrectomy. Is necessary treatment of complications in uveitis, cataract (surgery after reduction of inflammation), glaucoma, vitrectomy when needed.

Keywords Uveitis anterior · Uveitis intermediate · Uveitis posterior · Endoftalmitis

- Uveitis is inflammation of the uveal test (iris, ciliary body, choroid), often associated with inflammation of adjacent structures (cornea, sclera, retina, vitreous body).
- There are multiple classifications of uveitis, according to the single criterion or associated criteria.
- Classification based on the initial location of the inflammation: it is the anatomical classification according to the Standardization of Uveitis nomenclature SUN-2005.
  - **ANTERIOR UVEITIS**—iridocyclitis with inflammation of the iris and ciliary body equivalently which can be iritis, ***anterior cyclitis, or iridocyclitis***.
  - **INTERMEDIATE UVEITIS**—with the initial inflammation of the pars plana and external periphery.

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The term pars planita represents intermediate uveitis with vitreous condensation "snow lump" "ant owa" or "snow bank" sloping fibrinous exudate that marks the retina at 6 o'clock (with indentation).
Clinically, intermediate uveitis is ***pars planita, hyalit, or posterior cyclitis***.

- **POSTERIOR UVEITIS**—with initial inflammation located at the level of the retina and choroid that generates: ***multifocal focal choroiditis, chorioretinitis, retinochoroiditis, retinitis, or neuroretinitis***.
- **VASCULAR RETINITIS**—associated with periphlebitis venous vascular damage or periarteritis arterial which in AFG shows parietal impregnation and perivascular diffusion (leakage) and sometimes vascular occlusion generating retinal ischemia.
- **PANUVEITIS** with inflammation of the anterior chamber, vitreous, retina, choroid.

Anterior Uveitis (Table 11.1)

Etiology of Anterior Uveitis

- Infectious
  - Bacterial—syphilis, Lyme, Leptospira, leprosy.
  - Viral—HSV, HZV, CMV/HIV
  - Fungal
  - Parasitic—toxoplasmosis, toxocarosis, onchocercosis.

Table 11.1 Etiology of uveitis

Granulomatosis ant. uveitis	Nongranulomatous ant. uveitis	Intermediate uveitis	Posterior uveitis	Panuveitis
• Idiopathic • Sarcoidosis • HSV, HZV • TBC • Siphilis • Vogt–Koyanagi–Harada • Cytomegalovirus	• Idiopathic • HLA B27 – Ankylosing spondylitis – SD Reiter – Psoriasis – Crohn's disease – Hemorrhagic rectocolitis • Behcet • Leptospirosis • Uveitis in Rifobutin	• Idiopathic • Sarcoidosis • Multiple sclerosis • Syphilis • Lyme disease • TB	• Retinitis – Focal: Behcet, toxoplasmosis – Multifocal Necrosis: ARN, PORN, HSV, HZV, CMV, syphilis Non-necrotizing Bechet – Focal choroidites toxoplasmosis • Multifocal: birdshot, sarcoidosis, syphilis, TB	• Sarcoidosis • Toxoplasmosis • Endophthalmitis • Behcet • Syphilis • VKH • TB • Candidiasis • Sympathetic ophthalmia

- Spondyarthropathies: ankylosing spondylitis, Reitter.
- Systemic diseases:
  - Sarcoidosis, Behcet, juvenile idiopathic arthritis.
  - Rare—multiple sclerosis, Wegener, lymphoma.
- Ocular pathology
  - Pseudo uveitis heterochromica Fuchs.
  - Posner–Schosman syndrome
  - Iatrogenic–Rifabutin
- Pseudo Uveitis: retinoblastoma, leukemia, juvenile xanthogranulomatosis.
- Anterior uveitis is:
  - Granulomatosis: sarcoidosis, HSV, TBC, syphilis, leptospirosis, and brucella.
  - Nongranulomatous—HLA B27, trauma, drug-induced.

Etiology of Intermediate Uveitis (Including Pars Planita)

- Idiopathic
- Uveitis associated with systemic diseases.
  - Sarcoidosis
  - Multiple sclerosis
- Infecitous
  - Lyme disease, TBC
  - Richets–Brucella

Etiology of Posterior Uveitis

- Idiopathic
- Infectious
  - Bacterial: syphilis, lyme, TB.
  - Viral: HSV, HZV, CMV
  - Parasitosis: Toxoplasmosis, toxocarosis, onchocercosis.
  - Microzoa
- Uveitis associated with systemic diseases.
  - Behcet
  - Sarcoidosis
  - Multiple sclerosis

  - Vogt–Koyanagi–Harada syndrome
  - Collagenosis: SLE, scleroderma.
  - Wegener, periarteritis nodosa.
  - Systemic arteritis: Takayasu, Susac syndrome.
- Ocular
  - Birdshot retinochoroiditis.
  - White Spot Syndrome
  - Sympathetic ophthalmia.
- Pseudouveitis: Retinoblastoma, Hodgkin's lymphoma, non-Hodgkin's, metastases, paraneoplastic syndrome.

Etiology of Panuveitis

- Idiopathic
- Uveitis associated with systemic diseases.
  - Behcet
  - Sarcoidosis
  - Vogt Koyanagi Harada
- Infectious Uveitis
  - Toxoplasmic Retinochoroiditis
  - TB
  - Acute Retinal Necrosis
  - Bacterial Infections
- Ocular: sympathetic ophthalmia.

Pediatric Uveitis (Table 11.2)

Table 11.2 Pediatric uveitis

Anterior uveitis	Intermediate and posterior uveitis
• Idiopathic juvenile arthritis • Sarcoidosis • Heterochromia fuchs • HLAB27 spondyloarthropathies • Pseudouveitis – Retinoblastoma – Leukemia – Juvenile xanthogranulomatosis	• Toxoplasmosis • Toxocariasis • Lyme disease • Sarcoidosis • Intraocular foreign body • Pseudouveitis – Retinoblastoma – Leukemia – Lymphoma

Uveitis in the Elderly [1–9]

Unilateral Uveitis

- Anterior, postoperative, cataract
- Posterior
  - Toxopolasmosis
  - RNA (HZV, HSV)
- Bilateral uveitis
  - TB
  - Birdshot
  - Corticosteroid syndromes masked in...

    Lymphoma
    Whipple
    Cancer
- Uveitis with hypopyon
  - Behcet
  - HLA B27
  - HSV, HZV
  - Endophthalmitis
- Uveomeningitis
  - VKH
  - Behcet
  - Syphilis
  - Lyme disease
  - Sarcoidosis
  - Sympathetic ophthalmia
- Hypertensive uveitis
  - HSV, HZV
  - Heterochromia Fuchs
  - Sarcoidosis
  - Ankylosing spondylitis HLA B27
  - Posner–Schlosman
  - Toxoplasmosis
  - Syphilis
  - Idiopathic juvenile arthritis
- Uveitis without synechia
  - Birdshot
  - Iris Heterochromia Fuchs

- Posner Schlossman
- Intermediate uveitis

Etiological Classification of Uveitis is a clinical classification and represents the ocular etiology that produces… (Table 11.2)

- Infectious Uveitis: Bacterial, viral, fungal, and parasitic.
- Non-infectious Uveitis: With or without systemic diseases.
- Pseudouveitis: masked neoplastic syndrome or not.

Semiological Classification of uveitis associates the following ophthalmological signs and is…

- ***Uveitis associated with the Perikeratic Circle***
  - Keratitis in: HSV, Syphilis, TB, bacteria generating Kerato-Uveitis.
  - Scleritis and retinal vasculitis.

    Infections—HSV, HZV, TB, Lyme Disease
    Granulomatous diseases—sarcoidosis
    Sponduloarthropathies
    Systemic vasculitis—Wegener, Rheumatoid polyarthritis, Behcet, Periarteritis Nodosis.

- ***Uveitis associated with retro-corneal precipitates***
  - Large, granulomatous, "sheep fat"—sarcoidosis, syphilis, TB, leprosy, toxoplasmosis, VKH, lymphoma, "confluent sheep fat"—HSV.
  - Small, round, regular—Vogt Koyanagi Harada
  - In the form of spicules—Heterochromia Fuchs

    The fine precipitates are composed of neutrophils and lymphocytes, the "mutton fat" of macrophages and giant cells.
    The precipitates in HSV are fine at the beginning, they become granulomatous in the absence of treatment.

- ***Uveitis associated with Iris Signs***
  - Iris Nodules—Koeppe nodules (on the Irian sphincter) and Busacca (on the Irian cholera in: Sarcoidosis, TB, Syphilis).
  - Iris atrophy

    In the HSV sector.
    Diffuse to the sphincter and iris collarette in Fuchs heterochromia.

  - The Iris Synechites

    Anterior—Adherent between iris and cornea—in trauma.
    Angular—Adherent in the nails.
    Posterior—Adhesions between the iris and lens in anterior uveitis, absent in posterior uveitis, exceptional in primitive ocular lymphoma.

- ***Uveitis associated with Hopopion***
  - Spondyarthropathies: Reiter's ankylosing spondylitis, Crohn's Disease.
  - Behcet
  - Infections
  - Neoplasms: Leukemia, Retinoblastoma
- ***Uveitis associated with intraocular hypertension:*** *Toxoplasmosis, HSV, Ankylosing Spondyloarthropathy, Sarcoidosis, TB, Posner-Schlossmann.*

Classification of Uveitis According to Evolution

- ***Acute Uveitis***—Uveitis that has brutal onset and has a short duration of evolution—less than 3 months in...
- Anterior uveitis secondary to infections, ankylosing spondylitis HLA-B27, HSV, Toxoplasmosis.
- VKH syndrome
- White spot syndrome
- Plaque epitheliopathy, serpiginous choroiditis.
- Endophtalmitis
- ***Chronic Uveitis*** with progressive onset, is the intraocular inflammatory process prolonged over 3 months.
  - Idiopathic juvenile arthritis
  - Birdshot retinochoroiditis
  - Intermediate Uveitis—pars planned
- ***Recurrent Uveitis***—acute pustules separated by periods of inflammatory inactivity lasting more than 3 months. With an insidious onset, sometimes acute or subacute with exacerbation of inflammation.

Classification of Uveitis According to the Pathogen Agent [10]

- ***Exogenous Uveitis***—are produced by ocular invasion with microorganisms from the surface of the eyeball through...
- Perforated Corneal Ulcer
- Postoperative: cataract, glaucoma, DR.
- Perforated wound
- ***Endogenous Uveitis***—are produced by microorganisms or other agents inside the patient's body through...
  - Infection with bacteria (TB), fungi (candida), viruses (HZV), protozoa (toxoplasma), and roundworms (toxocara).
  - Uveitis associated with systemic diseases: sarcoidosis.
  - Idiopathic Uveitis

    Specific: heterochromia fuchs
    Non-specific

Clinical Signs depending on the location of Uveitis (Table 11.3)

Table 11.3 Clinical Signs depending on the location of Uveitis [3]

Anterior uveitis	Intermediate uveitis	Posterior Uveitis	Panuveitis
• Corneal edema • Cloudy AU • Hypopyon • Precipitated • Retrocorneal • Exudation in the pupil • Posterior synechiae • Complications: cataract, secondary glaucoma.	• Deposits with the appearance of "ant eggs" in the lower part of the ciliary body • Peripheral hyaline with "snowball" opacities • Peripheral retinal periphlebitis • Discreet signs of anterior uveitis	• Hyalitis—Choroiditis with single or disseminated foci in the form of well-defined yellow or gray spots that do not mask the vessels • Retinitis with retinal edema and ill-defined whitish spots covering the vessels • Vasculitis with white perivascular sheaths	Variable antigers at the three levels

Anterior Uveitis: Iridocyclites

Anterior uveitis (idichocyclitis) can be… [4]

- Nongranulomatous anterior uveitis is the most common [11]
  - Acute nongranulomatous iridocyclitis—the most common.

    Bacterial, viral, parasitic infections, mycoses.
    Associated with HLA B27.
    Ankylosing spondylitis
    Reiter syndrome
    Crohn's disease
    Ulcerative colitis

  - Chronic nongranulomatous iridocyclitis

    It has a longer duration of evolution with exacerbations and relapses.
    It is common in: juvenile arthritis and Fuchs heterochromic idicocyclitis.

  - Granulomatous anterior uveitis [12]

    It is characterized by the presence of nodules.
    Clinical forms can be acute and chronic.
    The most common granulomatous uveitis are TB iridocyclitis and Besnier, Boeck–Schaumann disease (Sarcosis).
    Granulomatous uveitis is present in Sarcoidosis, TB, syphilis, leprosy, VKH, CMV, and sympathetic ophthalmia.

    Differential diagnosis nongranulomatous/granulomatous uveitis (Table 11.4).

Table 11.4 Differential diagnosis nongranulomatous/granulomatous uveitis

	Nongranulomatous uveitis	Granulomatous uveitis
Debut	Acute	Insidious
Evolution	Short	Long
Red eyes	+++	+
Pain	+++	+
Iris nodules	–	+++
Corneal precipitates	Small	Large "mutton fat"
Posterior synechiae	Thin	Large, thick
Posterior pole	Diffuse affect	Nodular lesions

  - Clinical symptoms of anterior uveitis with eye pain, red eye, photophobia, epiphora, are very important in the current form, but can be minimal or absent in the chronic form.

The symptoms and clinical signs in a uveitis are related to the acute or chronic nature of the previous uveitis, but also to the granulomatous, non-granulomatous type.

Acute Anterior Uveitis [13, 14]

- Clinical Symptoms
- ***Pain***
- Is the dominant symptom in acute uveitis
- It has a pulsating character of variable intensity, it is spontaneous or caused by pressure on the eyeball.
- It worsenes at night, intermittently or continuously.
- It radiates in the territory of the trigeminal nerve towards the forehead, scalp (related to the irritation of the ciliary nerves).
- It is accentuated by light, excessive accommodation, and palpation of the eye.
- ***Red Eye***—Intense perikeratic conjunctival hyperemia produced by active hyperemia of the anterior ciliary vessels.
- ***Photophobia and blepharospasm***—produced by irritation of nerves V and VII.
- ***Lacrimation***—Mediated through Afferent nerve V and Efferent nerve VII.
- ***The variable decrease in vision through...***
  - Changes in the transparency of the cornea and the anterior chamber.
  - Ciliary spasm myopia.
  - Exudates in the pupil, cyclic membrane.
  - Decrease of the transparency of the vitreous body.
- Complications: Cataracts, Secondary Glaucoma, Cyclic Membrane, Macular Edema, Papillary.
  - Clinical Signs [13, 15, 16]

- In daylight.
  - Red eyes with conjunctivitis and dilated episclerals.
  - Pseudoptosis due to photophobia and palpebral edema.
  - Irregular pupil with iridocrystalline synechiae.
- In the microscope.
  - ***Severe palpebral Edema*** in acute uveitis.
  - ***Intense perikeratic conjunctival*** hyperemia in acute uveitis, minimal in chronic form (required differential diagnosis with peripheral hyperemia from conjunctivitis).
  - ***Cornea*** (Fig. 11.1)
- Endothelial corneal edema accentuated if uveitis is accompanied by increased IOP.
- Retro-corneal keratic precipitates arranged lower triangularly with the tip at the center of the cornea (Fig. 11.2)
  - Small, medium—are present in acute, chronic non-granulomatous uveitis.
  - Redness—in hemorrhagic uveitis.
  - In "mutton fat"—in granulomatous iridocyclitis, the recent precipitates are whitish with blurred edges, the old ones are pigmented, irregular, well outlined.
  - Multiple small "endothelial dust" precipitates in acute anterior uveitis and chronic uveitis exacerbations.
- **Exudative changes in the anterior chamber.**
  - Tyndall cell, Tyndall positive.
  - Hypopyon—serous, serofibrinous, purulent exudate deposited in CA.

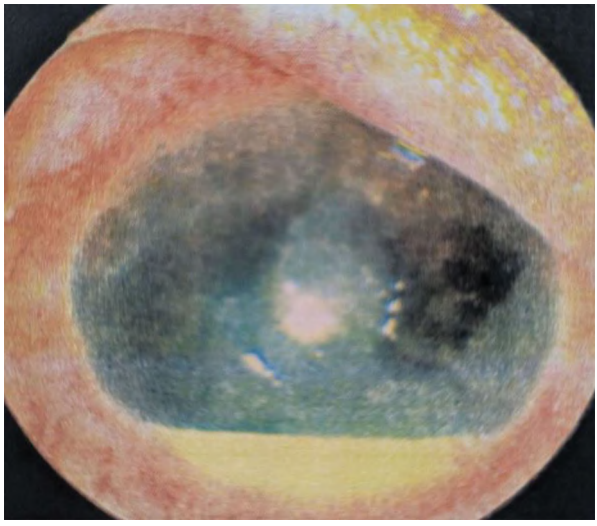

Fig. 11.1 Acute keratoiridocyclitis with hippropion

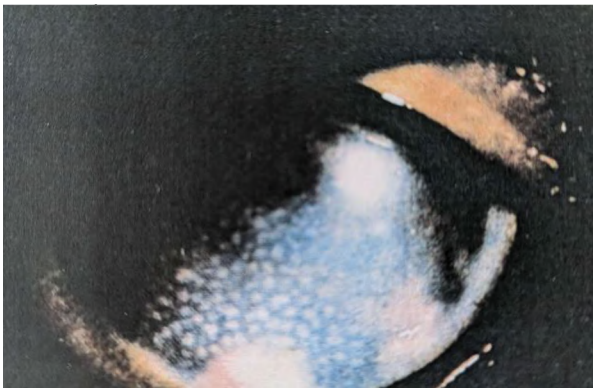

Fig. 11.2 Iridocyclitis with precipitate

  - Exudation in the pupil on the anterior crystalloid with posterior irionic synechiae.
  - Changes in the corneal angle with cellular deposits, goniosynechiae.

- **Iris signs** with edematous iris in acute or atrophic uveitis in chronic forms.
  - Color changes with hyperpigmentation in acute form and depigmentation in evolution.
  - Iris nodules in granulomatous uveitis: Koeppe nodules on the edge of the pupil and Busacca nodules on the anterior face of the iris near the collarette. They are present in sarcoidosis, TB, VKH, fuchs, and syphilis.
  - The posterior iris synechiae are adherent between the posterior surface of the iris and the anterior capsule of the lens and its anterior hyaloid (at afac): the synechiae can be: segmental, annular that form a "bulging iris" with increasing IOP, seclude the pupillary + exudative membrane in the pupillary field, seclusion/pupillary occlusion.
  - Neovascularization of the iris—rubeosis iridis developed in some forms of chronic iridocyclitis.

- Pupillary signs
  - Regular/irregular spastic miosis with RFM present slowly.
  - Pupillary ectropion
  - Pupil with irregular contour due to the formation of posterior synechiae.
  - Slow or absent pupillary reaction.
  - Pupil occlusion—organized exudate in the entire pupillary area.

- Changes in the lens
  - Pigment dispersion on the anterior crystalloid.
  - Exudates on criatalin in acute fibrino-plastic iridocyclitis.
  - Complicated cataract with polychromatic or posterior subcapsular appearance, rapidly progressive.

- Vitreous changes with the presence of inflammatory cells and vitreous exudates in acute iridocyclitis.
- The ophthalmological clinical examination will be completed with tonometry, gonioscopy, and ophthalmoscopy.

Differential diagnosis of acute anterior uveitis (iriocyclitis) (Table 11.5)

- Positive diagnosis—it is determined by correlating subjective symptoms with objective signs. To establish the etiological diagnosis, the clinical examination is correlated with the complete paraclinical investigation, with laboratory and imaging examination.
- The most frequent causes of Acute Uveitis are…
  - Idiopathic, frequently associated with HLA B27.
  - Spondyarthropathies: ankylosing spondylitis, Reiter's syndrome.
  - Inflammatory bowel diseases: hemorrhagic rectocolitis, Crohn's disease.
  - Other causes: sarcoidosis, Behcet's disease, HSV, HZV, Syphilis.

Table 11.5 Differential diagnosis of acute anterior uveitis (iriocyclitis) [17]

	Acute conjunctivitis	Acute iridocyclitis	Acute glaucoma
Debut	Progressive	Prequently progressive	Brisk
Pain	Uncomfortable foreign body sensation	Moderate eye pain extended in the area of the first V branch	Severa in the eyes and area of the Vth nerve
Secretions	Mucopurulent	Aqueous	Aqueous
Colored halos	–	Absent	Present
Conjunctival congestion	Light red peripheral conjunctival hyperemia	Deep red conjunctival hyperemia, perilimbic violet	Deep red, violet conjunctival hyperemia
Anterior media	Clear	Disturbance of transparency through precipitates and exudates	Disturbance of transparency due to corneal edema
Cornea	Normal	• Retrocorneal precipitates • Corneal edema • Descenmetic folds	Corneal edema
AC	Normal	Normal	Small
Pupil	Normal	Small, unregulated	Mydriasis, areflexive, vertical oval
Iris	Normal	Muddy homogenized	Edematous
IOP	Normal	Frequently normal	Enlarged
General signs	Absent	Small, present depending on the etiology	• Prostration • Vomiting

Chronic Anterior Uveitis [16]

- Positive diagnosis: clinical signs and symptoms: moderate redness.
  - Small and medium-sized retro descemetic precipitates.
  - Precipitated in "mutton fat" in granulomatous inflammations.
  - Small Koeppe nodules located on the edge of the pupil and larger and more peripheral Busacca nodules.
- Important causes of chronic anterior uveitis
  - Fuchs uveitis
  - Sarcoidosis
  - Idiopathic juvenile arthritis
  - VKH
  - TB

Clinical Forms of Uveitis After Exudation

- Fibrinoplasty form
  - Early fibrinous exudate in CA, pupil, iridocorneal angle.
  - Posterior iris synechiae with pupillary seclusion.
  - Seclusion/pupillary occlusion with UA blockage in CP and increased IOP with secondary glaucoma.
  - More common in rheumatic iridocyclitis in the elderly and streptococcal iridocyclitis in children.
- Serous form
  - Of viral etiology
  - Precipitation on the posterior surface of the cornea.
- Hemorrhagic form—with hyphema, rarely, in: viral infections, diabetics, Behcet, Harada, TB.

Recurrent Uveitis

- Neganulomatous
  - Associated with HLA-B27
  - Idiopathic Juvenile Arthritis
  - Fuchs Heterochromia

- Granulomatous
  - Sarcoidosis
  - TB milestones

Chronic Cyclitis [5]

Chronic Cyclitis is only in iris inflammation.

Clinical Signs
- Eye completely calm
- Precipitation on the posterior surface of the cornea
- Fine exudates in CA and vitreous body.
- Peripheral posterior synechiae.
- Retrocrystalline exudative membrane.

Symptoms
- They are limited most of the time to the decrease in the variability of the VA.

The differential diagnosis of iridocyclitis requires...

- The differential diagnosis of red eye: acute glaucoma, conjunctivitis, iridocyclitis.
- Differential diagnosis between granulomatous and non-granulomatous forms.
- Etiologic differential diagnosis

Complications and checks in Uveita [18, 19]

- ***Complicated cataracts***—It is the most common complication of irichocyclitis and more frequently affects the posterior subcapsular cortical layers.
- ***Secondary glaucoma***
  - Early—**hypertensive uveitis**: they occur in the acute phase of the disease by excluding from the anterior chamber, the iridocorneal angle that blocks the drainage of the aqueous humor in the pupil and at the trabecular level.
  - Late—**post-inflammatory glaucoma** is produced by...

    Pupillary block by pupillary seclusion given by annular synechiae or pupillary occlusion by the organization of the exudate, which prevents the flow of UA between CA and CP.
    Trabecular blockage by goniosynecies (anterior peripheral synechiae).
    Iatrogenic through prolonged cortisone treatment.
- ***Cyclic membrane***—formed by the fibrosis of the exudates present in front of the lens. It is a late complication of the form of acute plastic iridocyclitis.
- ***Choroiditis*** develops in prolonged forms of iridocyclitis.
- ***Retinal complications***
  - Cystoid macular edema
  - Macular degeneration

  - Exudative or secondary retinal detachment
  - Papillitis can be present in severe forms of iridocyclitis.

- **Band keratopathy**—present in chronic uveitis in still's disease in children.**The clinical aspect of uveitis according to etiology**

Juvenile Chronic Arthritis [20]

- Child (girls > boys)
- Oligoarticular form 50%, rarely polyarticular form.
- Systemic still form—absent uveitis
- Clincal
  - Non-granulomatous anterior uveitis, synechiant, chronic, bilateral.
  - Asymptomatic at onset
  - Antinuclear antibodies present (ANA positive)
- Prognosis—reserved
- Complications
  - Keratitis in the strip
  - Iridocrystalline synechiae

Fiessinger Leroy Reiter Syndrome

- Patient with inflammatory lumbar joint pain and tendinitis
- Urinary signs: urethra, genital or digestive infections precede uveitis by several weeks.
- Clinical
  - Acute nongranulomatous anterior uveitis
  - Iridocrystalline synechiae
- Laboratory—HLA B27

Behcet Syndrome

- General: mucosal skin signs with: oral, genital canker sores, erythema nodosum, joint lesions, neurological signs, thrombotic complications.
- Clinical
  - Anterior uveitis with nongranulomatous hypopyon.
  - Ocular hypertension due to pupillary block.

  - Secondary Cataracts
  - FO: hyalit, retinitis, vasculitis (dead tree appearance of the arteries).
- Laboratory: HLA B27
- Prognosis—reserved with sequelae and neuro-ophthalmological damage.

Heterochromia Iris Fuchs

- Youth
- Clinical
  - Unilateral Uveitis, with chronic evolution.
  - Evenly distributed pigment precipitates.
  - Fine protein tyndal.
  - Irian heterochromia, sometimes round nodules.
  - Posterior subcapsular cataract.
  - Anterior hyalitis (myodesopsia).

Lyme Disease [21]

- Evolution
  - Primary phase—chronic migratory erythema.
  - Secondary phase—Arthritis, cardiac touch, radiculitis, paralysis of nerve VII.
  - Tertiary phase—chronic atrophic acrodermatitis.
- Benign cutaneous lymphocytoma.
- Clinical
  - Anterior and intermediate uveitis
  - Conjunctivits
  - Papilitis
  - Optic Neuropathy

Sympathetic Ophthalmia

- Posttraumatic or postsurgical uveitis in the second eye.
- Clinical
  - Granulomatous Bilateral Uveitis
  - Hyalitis, choroidal infiltrate with characteristic Dalen Fuchs pseudo nodules (yellow pigment infiltrate in the periphery).

Posner–Schlossman

- Youth, more frequently in men.
- Evolution in recurrent cases.
- Clinical
  - White eye, slightly painful, unilateral, with foggy vision.
  - Central white precipitates surrounded by small satellite precipitates.
  - Nongranulomatous Uveitis
  - Ocular hyperopia preceded by inflammatory signs: epithelial corneal edema (related to intraocular hypertropin).
- Iridocorneal angle—open
- Never the posterior irian synechiae.

Sarcoidosis

- Young, more common female with pusee-evolving disease
- Clinical
  - Anterior, bilateral, chronic, granulomatous uveitis
  - Precipitate in broad, "sheep fat" in the lower cornea
  - Koeppe nodules on the pupillary margin or Busaca in the Irian stroma,
  - Nodules in the iridocornean angle
  - Sometimes acute or intermediate negranulomatous anterior uveitis
- Laboratory
  - Angiotensin converting enzyme
  - Hypercalcaemia, tuberculin anergy
- C. T. chest scan
- Respiratory examination with bronchoalveolar lavage and bronchial biopsy or ganglion (granuloma)
- Conjunctival biopsy of lacrimal or salivary glands
- General
  - Cutaneous sarcoid erythema nodosum
  - Lacrimal and/or salivary gland hypertrophy
  - Lymphadenopathy
  - Polyartralgia
  - Cranial neuropathy with meningeal touch
- **Spondylarthropathies**
  - Youth, more common male sex.
  - Clinical

Anterior, unilateral, relapsing uveitis
Irido-crystalline synechia
Fibrinoplastic uveitis with hypopion
HTIO
Hyalitis, posterior uveitis, Cystoid macular oedema
Laboratory
HLA-B27 present
Sacroiliac and lumbar radiography

- Possible recurrences, sometimes frequent
  - **Syphilis**

    Clinical forms

    Primary-chance
    Secondary-roseola
    Tertiary

    Mucous, cutaneous, visceral Goma
    Tables, PGP

    Clinical

    Uni, bilateral
    Granulomatous anterior uveitis or not
    Keratitis, scleritis
    Disseminated multifocal chorioretinitis
    Neuroretinitis
    Pars planita

    Laboratory-serology++

    Toxoplasmosis

    Unilateral frequent
    Clinical

    Anterior uveitis with lower precipitate with HTIO or not
    Chorioretinitis with white retinal focus with possible other cicatricial pigmented foci.

  - **Tuberculosis**

    Clinical

    Granulomatous uveitis
    Retinal vasculitis, peripheral
    Tuberculoma
    Military choroid foci

    Laboratory—tuberculin idr

- **Vogt-Koyanagi-Harada**

  General

  Vitiligo, poliosis, alopecia, hearing loss
  Neurological signs with meningeal syndrome

  Clinical

  Bilateral, granulomatous anterior uveitis
  Intraocular hypertension +
  Posterior synechiae
  Posterior damage

  Laboratory

  Lumbar puncture-lymphocytic meningitis
  Audiogram-hearing loss

  Stage evolution

  Prodrome with neuromeningeal signs
  Acute uveitic phase
  Convalescence phase (uveal depigmentation)
  Chronic recurrence phase

- **HSV** [22]

  Anterior uveitis with pusee progression, with possible relapses
  Clinical

  Granulomatous or not precipitated anterior uveitis retrodescemetics throughout the cornea
  Keratouveitis (affected endothelium)
  Irian atrophy in the sector
  +-corneal anesthesia
  Retinitis (eliminates RNA)

  Possible association with skin rashmucous.

Treatment of Uveitis

- **Treatment of uveitis is difficult and often is a treatment symptomatic, deprived of the opportunity to limit relapses.**
- Treatment of uveitis has the following goals
  - Improved vision
  - Removal of pain
  - Prevention of complications and sequelae
  - Decreased intraocular pressure (IOP) if secondary glaucoma occurs

Treatment of Anterior Uveitis

- Treatment of anterior uveitis is predominantly topical with Mydriatic, cycloplegics, corticosteroids (topical and parabulbar), NSAIDS, as needed Systemic with corticoids and antibiotic.
- Treatment of posterior uveitis is predominantly systemic depending on etiology.

Physical Measures

- The application of dry heat locally lessens pain, increases circulation, reduces venous stasis and dilutes toxins.
- Colored lenses (sunglasses) reduce photophobia, lacrimation, blepharospasm.

Mydriatic and Cycloplegic Treatment

- Reduces inflammation through mydriasis and cycloplegia
- Relieves pain by blocking Irian and ciliary body spasm
- Reduces exudation and prevents the adhesion of the iris to the lens with preventing the formation of Irian synechia or breaking them by collars, Mydriatic-atropine, phenylephrine, or subconjunctival injections—adrenaline (if needed)
  - cycloplegic and Mydriatic agents used in topical administration are: atropine solution 1%, 0.5%, homatropine—cholir 1%, scopolamine—0.25–0.50%, cyclopent-cholir 0.5–1% solution, adrenaline (epinephrine)—cholir or subconjunctival injections, neosinephrine (strong Mydriatic, without cycloplegic effect);

    short action-tropicamide 0.5–1%, cyclopentolate 0.5–1%, phenylephrine 2.5–1%
    long action-atropine 1%—duration of action 6–10 days.

Corticotherapeutic Treatment

Corticotherapy in local and systemic treatment reduces inflammation, decreases vascular permeability, reduces exudation.

Topical Steroids

- **Represents the medication of choice in anterior uveitis** the frequency of topical administration of corticosteroids is variable:

- at onset in acute forms, corticoids are administered every 15 min for several hours, then 4 times/day
- for medium forms 4 times/day, diminishing, with stop in 5–6 weeks
- for severe forms, hourly administration

Periocular Steroids

- If severe forms of uveitis do not respond to topical treatment, resort to periocular and/or oral injectable treatment.
- previous subthenon injections with beta-metasone CELESTONE, 0.5 ml, AC 25 g posterior with triamcinolone KENACORT, methylprednisolone DEPO-MEDROL 1 ml with 25 g needle
- **Subconjunctival or laterobulbar injections after topical anesthesia, subtenon injection indicated in posterior uveitis**
- Triamcinolone

Intraocular corticoids are indicated in: serious posterior uveitis associated with Cem (intravitreal triamcinolone 4 mg/0.1 ml) intermediate, posterior uveitis-intravitreal implants-RETISERT

General corticoid treatment is indicated in: anterior, intermediate, posterior uveitis unresponsive to treatment topical, intratenonian, severe posterior uveitis with decreased acuity visual and macular edema, occlusive vasculitis and serous retinal detachment, anterior uveitis associated with extraocular manifestations (Behcet, VKH etc.), bilateral uveitis, panuveitis.

General cortisone treatment has action [23]:

- Anti-inflammatory and antiexsudative
- Immunosuppressants by inhibition of immunoglobulin synthesis

Oral corticotherapy—Prednisone

- 1 mg/kg/day, one outlet in the morning
- Progressive decrease for several weeks, which is not necessary, if cortisone treatment is less than 2 weeks
- Potassium supplementation
- Salt-free and sugar-free diet with fast absorption
- Associated with omeprazole if there is a history of gastric ulcer.

CORTISONE TREATMENT NEVER STOPS because it can generate severe sudden onsent REBOUND of inflammation.

Intravenous corticotherapy (bolus)

- Methylprednisolone-Solu-MEDROL
  - 500–1000 mg/day
  - 1 bolus/day in 3–6 h, for 3 consecutive days
  - potassium substitute

- Prednisone-CORTANCYL—1 mg/kg/day
- Surveillance
- Clinical
  - blood pressure control during infusion and 30 min after, then every 6–6 h until the next infusion
  - control of the neuro-psychic state
- Biological
  - Glycemia
  - HbAIc in diabetic or non-diabetic patients
  - ECG

Complications of Cortisone Treatment (Table 11.6)

Nonsteroidal anti-inflammatory drugs-NSAIDs

- NSAIDs are used in uveitis for their anti-inflammatory potential, and have major indications in uveitis associated with rheumatoid diseases.
- Topical NSAIDs in combination with topical steroids reduce the duration of corticosteroid therapy.
- NSAIDs are adjuvant drugs in the treatment of trenant uveitis.
- Topical NSAIDs: Voltaren, Diclofenac, Indocolir, Naprosin, Ocufen, Pranoflog.
- Systemic NSAIDs: aspirin 1 g/day, paduden, brufen, indocid, voltaren, phenylbutazone, percluson, tanderil, tomadol, piroxicam.

Antibiotic Treatment

- It is indicated in endogenous uveitis, triggered and maintained by bacteria, viruses, fungi, parasites, but also in acute infectious endophthalmitis.
- Antibiotics should be used depending on the etiology of uveitis, and whether it is possibly after the antibiogram.
- Antibiotics
  - subconjunctival: gentamicin, cephalosporin, vancomycin, bacitracin, polymyxin, colimycin
  - retrobulbar-ampicillin, gentamicin
  - washing CA-gentamicin, penicillin, polymyxin, ampicillin, chloramphenicol
  - injections I.v., I. m.—tobramycin, cephalosporins III generation, gentamicin.

Table 11.6 Complications of cortisone treatment

Topical therapy	Systemic treatment	
IOP growth	Sodium retention	Seizures
Posterior cortical cataract	Hyperglycemia	Mental disorders
Bacterial superinfeciton	Peptic ulcer	Osteoporosis
Fungous	Hirstuism	Cushing's syndrome

Immunosuppressants

- Are indicated in the treatment of severe corticoresistant uveitis in which steroids they have insufficient or ineffective action and there is a danger of blindness.
- Their administration is carried out with hematological, oncological supervision.
- They are used in diseases of the system, with immune damage: Behcet's disease, sympathetic ophthalmia, pars planite, VKH, retinal vasculitis.
- Methotrexate, azathioprin (imuran), mycophenolate mofetil, cyclosporine, tacrolimus.

Treatment of Complications

- Postinflammatory glaucoma-hypertensive uveitis
- Timolol 0.5% 2/day
- Acetazolamide 250 mg 3/day
- Pilocarpin and latanoprost are contraindicated
- Postinflammatory glaucoma with posterior synechiae
- Laser iridotomy (in ring synechiae) at need iridectomy under high doses of cortisone
- Complicated cataract—surgical extraction of the lens performed with caution, the presence of precipitates contraindicated for surgery.
- Retinal detachment
  - Exudative-clinically followed
  - Tractional-surgical intervention
- Preatrophic globe-enucleation if the eye is sore.

Intermediate Uveitis: Planeed PARs

- Are primary inflammations of the uvea located at the level of the anterior vitreous and peripheral retina (base of the vitreous)..
- They can be bilateral, asymmetrical, more often affecting women (young adult).
- The course of intermediate uveitis is prolonged, accompanied by relapses relatively frequent that require prolonged corticotherapy, with its consequences.
- Common causes of pars planitis
  - Idiopathic
  - Plaque sclerosis
  - Sarcoidosis
  - Lyme disease, Whipple

Symptoms

- The ailment has insidious onset, with the cessation of vision and the appearance of flies volante-myodepsis
- Mild pain, photophobia, rarely
- Visual acuity is further reduced by complications: EMC, keratopathies in the band, cataract
- Nocturnal cecity
- Transient myopia.

UNTREATED OR POORLY TREATED INTERMEDIATE UVEITIS has reserved visual prognosis

Objective Signs

- Exam in daylight
- white eyes without signs of inflammation
- normal pupil with RFM, rarely modified
- Anterior segment biomicroscopy—minor signs of anterior uveitis with retrocorneal precipitates and posterior synechiae
- Indirect ophthalmoscopy and biomicroscopy with Goldmann lens with Pupil dilated and indentation.
  - at the level of 6 h, at the base of the vitreous slightly protruding whitish plates with appearance "ant eggs"
  - yellowish-white inflammatory aggregates in the periphery of the retina with the appearance of "snow ball lumps" or grey-white placard at the lower pars plana level "snow bank" (snow banking)
  - rear take-off of vitreous
  - peripheral perivascularitis of the choroid, with vascular thrombosis and foci of peripheral choroiditis
  - peripheral neovascularization that can generate fibrovascular tracts with annular peripheral retinal detachment
  - Cystoid macular oedema (rare)
  - papillary oedema
- Gonioscopy reveals anterior peripheral synechia and neovascularization.
- Intraocular pressure-TIO-secondary glaucoma may occur, through prolonged course of the disease, but also with cortisone treatment,
- Evolution: 10% self-limitation, 60% prolonged development, 30% with exacerbation.
- Complications: band keratopathy, cyclitic membrane, subcapsular cataract posterior, secondary glaucoma, vitreo-Retinal interface syndrome, Cem, retinal detachment.
- Treatment
  - corticosteroids locally and systemically can control acute outbreaks and reduce inflammation
  - periocular injections of steroids that can prevent complications of prolonged corticotherapies
  - suggested dose 0.5 cc methylprednisolone, alternating with 0.5 ml triamcinolone at 1–2 weeks
  - If it does not respond to steroids systemically, immunosuppressants are indicated (methotrexate, azathioprin, cyclosporin or antimetabolites).

Posterior Uveitis

- Are inflammations of the choroid and retina in which there may also be a touch anterior, transient uveal.
- The discovery of the disease is made under variable conditions faster when there are an interest in the macula.
- The causes of posterior uveitis can be: toxoplasma, toxocara, HSV, Treponema, histoplasm, Lyme disease, sympathetic ophthalmia.
- Clinical forms
  - Suppurative choroiditis—with purulent inflammation of the choroid-endophthalmitis
  - Non-suppurative choroiditis, negranulomatous or granulomatous, uni-/bilateral

    morphologically it can be diffuse, disseminated and circumscribed (focal) focal lesions may be localized

    central, macular in toxoplasmosis, TB, syphilis, histoplasmosis, rarely in larva migrans
    juxtapapillary in Jensen choroiditis
    in the peripheral choroid anterior to the equator in syphilis
    Equatorial

- Symptoms
  - decreased vision to varying degrees depending on the degree of impairment of vitreous, retina and choroid, extent and location of lesions
  - visual acuity decreases dramatically if the macula or beam is affected papillo-macular
  - myodesopsies (fly flies)
  - metamorphopsies-image distortion
  - micro-, macropsia
  - positive scotoma
- **Clinical signs** [3]
  - fine precipitate if cyclitis is associated
  - fine or dense vitreous opacities, + fibrillar or membranous condenses localized in the middle or posterior vitreous
  - rear vitreous take-off
  - FO highlights:

    foci of choroiditis with deep, well-delineated grayish-yellow spots, not covering the vessels of the retina
    foci of retinitis with yellowish-white placards covering the vessels followed in evolution of white chorioretinian atrophy with pigmented edges
    periphlebitis, rarely, periarteritis in the form of white sleeves that surrounds the vessel which sometimes in the scarring phase can sclerosis

neovascularisation (in sarcoidosis) which may be complicated by haemorrhage vitrean
DR regmatogenic in toxoplasmosis or exudative in VKH
papulitis, optic atrophy
granuloma in sarcoidosis
retinal lesions can be focal or multifocal

- Complications
  - extension of inflammation to the anterior uvea
  - cataract
  - degeneration of the vitreous
  - macular oedema
  - epiretinian membrane
  - venous occlusion
  - choroidal neovascularization
  - retinal detachment
  - optic neuropathy

Treatment of posterior uveitis—Treatment of posterior uveitis is similar to anterior uveitis

- Nonspecific treatment
  - topical and systemic with corticoids
  - subtenon injections with corticosteroids are useful in the acute phase of posterior uveitis
  - systemic with corticoids
  - immunosuppressants are necessary in some forms of posterior uveitis
- specific treatment is causal treatment where the etiology has been identified
  - toxoplasma
  - TB
  - syphilis
  - toxocara**Clinical forms of uveitis**

Uveitis and Rheumatic Pathology

Spondylarthropathies [15, 24]

- Ankylosing spondylitis [6]
  - HLA B27 positive 90%
  - Young male 20–40 years old, also present with family members
  - **Ocular**

Acute negranulomatous anterior uveitis 30%, sometimes recurrent or fibrino-plastic conjunctivitis
Peripheral corneal infiltrates
Papulitis
Good long-term ocular prognosis and rare complications [25]

General

Joint, bone symptomatology with sacroiliac joint inflammation and evolutionary axial skeleton up to immobilization
Treatment of anterior uveitis: indocid and aspirin, contraindicated, because they can increase recurrences.

Fiessinger–Leroy–Reiter syndrome

HLA B27 positive
Eyepiece

Mucopurulent conjunctivitis with chlamydia, shigella, salmonella) superficial punctate keratitis
Acute negranulomatous anterior uveitis in 20–30%
General-urethritis, arthritis

- **Psoriatic rheumatism**
  - HLA B27, HLA 17
  - **Eyepiece**

Acute anterior uveitis (10%)
Corneal infiltrates
Secondary SJM

Juvenile Idiopathic Arthritis [26]

- Present in child (2–16 years) more common in girls [20]
- **ocular**
  - chronic, negranulomatous, asymptomatic and bilateral anterior uveitis (70%) white-eyed
  - clinical forms of uveitis are varied from discrete forms (25%), moderate, severe, but responsive to treatment to severe forms (25%) with complications: band keratopathy, glaucoma, globe phthisia
- general
  - interests small and wide joints
  - fever
  - adenopathies
  - hepatosplenomegaly
  - pericarditis

- treatment [27]
  - topical: corticosteroids, NSAIDs, Mydriatic, cycloplegic
  - periocular cortisone injection
  - systemic: steroids, immunosuppressive therapy in corticoresistant patients
- mandatory monitoring of patients with periodic supervision
- risk factors
  - early onset (under 6 years)
  - pauciarticular touch (<5 joints)
  - positive antinuclear antibodies

Non-infectious Uveitis in Systemic Diseases [28, 29]

Behcet's Disease

- Multisystem idiopathic disease, affecting the young male with HLA B51 eye-piece, Hla B12 oral and skin, HLA B27 joints
- Eye disease is chronic, with a tendency to relapse and can lead to blindness by US or uveal, retinal damage
- Symptomatic triad
  - acute iritis with hypopion
  - oral thrush
  - genital ulcers
- Ocular
  - acute, relapsing, bilateral anterior uveitis + hypopion
  - posterior uveitis with transient dispersed retinal infiltrates, papillary oedema, occlusive vasculature, massive retinal exudation with progression to atrophy-optics, vascular obstructions, chorioretinal scar
- **General**
  - Cutaneous-mucous signs with mouth and genital aphthous lesions, erythema nodosum, folliculitis
  - Joint damage
  - Neurological signs
  - Thrombotic complications
- **Treatment**
  - systemic corticoids
  - immunosuppressants: azathioprin, infliximab, cyclosporine

Sarcoidosis [16]

- Pus disease, which affects the young adult more frequently
- **Ocular**
  - acute negranulomatous anterior uveitis in young adults with brutal onset with hilar adenopathy and erythema nodosum
  - chronic granulomatous anterior uveitis affects the elderly patient with chronic pulmonary sarcoidosis
  - intermediate uveitis 10–20% complications with: subcapsular cataract posterior Cem, papillary oedema, occlusive vasculitis
  - posterior pole damage: retinal periphlebitis, granulomas: choroid, retinal, papillary, preretinal (Landers sign), retinal neovascularization peripheral
  - Cystoid macular edema is the main cause of Av decrease in uveitis hindquarters
  - bilateral granulomatous panuveitis
  - follicles, conjunctival granulomas
  - scleral nodules
  - keratoconjunctivitis sicca
- General
  - 100% lung damage (pulmonary fibrosis)
  - adenopathies
  - hepatosplenomegaly
  - lacrimal gland damage, with enlarged and painful parotid gland
  - paralysis of cranial nerves
  - skin rash
- Treatment
  - Topical, systemic corticosteroids in high doses
  - Mydriatic, cycloplegic
  - Immunosuppressants in refractory cases: methotrexate, cyclosporine A

Vogt-Koyanagi Harada Syndrome (Fig. 11.3)

- Multisystemic condition that includes the skin, CNS and eye, manifested by diffuse uveitis severe, bilateral granulomatosis with retinal detachment serous associated with dermatological signs, CNS, acousticovestibular.

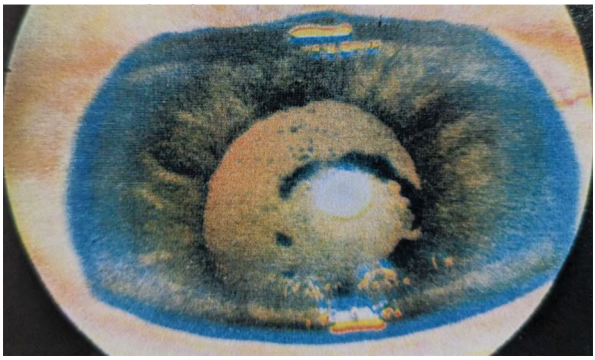

Fig. 11.3 VKH syndrome-acute iridocyclitis with pigment on the anterior crystalloid

Vogt-Koyanagi Disease

- Ocular—anterior uveitis with pusee evolution, with sechelar lesions
- General
  - meningeal signs
  - bilateral hearing loss
  - poliosis, alopecia, vitiligo

Harada Disease: Brutal Debut

- Ocular
  - eye signs appear 10–14 days after the onset of general signs
  - bilateral posterior uveitis
  - papillary oedema
  - lower retinal detachment at onset
- General
  - meningeal signs
  - encephalitic signs-hypertonia, NC paralysis, convulsion, delirium
- Treatment
  - topical steroids, systemic laterobulbar may give favorable ocular evolution, but long in refractory cases: cyclosporine, azathioprin, cyclophosphamide, chlorambucil

Viral Uveitis [30]

HSV

- HSV anterior uveitis is commonly associated with dendritic keratitis geographic, disciform, Associated or not with rash.
- HSV anterior uveitis is frequently acute, unilateral, hypertensive 40–90%, with precipitates, without cellular inflammation (Tyndall) in CA, with synechia (35%) recurrent.

HZV-generally affects elderly immunodepressed patients.

- Ocular
  - Typical lesions are keratitis, which can be associated with iritis especially in patients with vesicular rash in the nose area (Hutchinson sign)
  - Negranulomatous iridocyclitis with small, rare precipitates in "mutton fat", unobtrusively cloudy watery humor (rarely hemorrhage, hypopion).
  - Unilateral, hypertensive anterior uveitis
- Treatment

Treatment of viral uveitis is done with (Table 11.7):

- oral antivirals
  - Acyclovir = 800 mg 5/days to 6 weeks
  - Valaciclovir = 1 g 3/day
  - Famciclovir = 500 mg 3/day 3.4 weeks, combined with

Table 11.7 Treatment in uveitis and viral retinitis

Medicine	Dose	Secondary effects	Indications
Acyclovir	• Intravenously = 1500 mg/m^2/ day divided into 4 intakes, 14 days followed by: • oral = 800 mg 5 days 6 weeks • prophylactic = 400 oral	• Gastrointestinal impairments • Hypersensitivity • Renal dysfunction • CNS	• HSV1, HSV2 • HZV • EBV • CMV
Valacyclovir	• Oral anterior lg • 2G-post uveitis • Uveitis at 8 h, 6 weeks • Prophylactic 1 g/day	Similar to acyclovir	• HSV1, HSV2 • VZV ≥ CMV
Ganciclovir	• IV = 500 mg at 12 h 14 days • Intravitreal + 2–5 mg/0.1 ml • Topical gel 4/day, 3 months for CMV • Intravitreal implant—8 months	Anemia, thrombocytopenia, granulocytopenia	• HSV1 • CMV ≥ HZV
Valgancyclovir	• Oral 900 mg 3/6 weeks	• Gastrointestinal disorders • Medullary avection • Headache	• HSV1

- Mydriatic
- Topical corticoid treatment, all for a few weeks, then continue only with antivirals
- Treatment of ocular hypertonia is difficult, being aggravated by corticotherapy
- Surgical treatment, if necessary

PORN Syndrome (Progressive Outer Retinal Necrosis) [31]

It is present more frequently in immunodepressed, in AIDS with decreased vision bilateral, with minimal inflammation, in HZV infection

Clinical
- Retinitis with fulminant centrifugal extension
- Bilateral affection from the beginning
- Associated inflammation
  - Previous segment
  - Vitritis
  - common papulitis
  - Possible serous DR
  - The macular edema sometimes

RNA Syndrome [31]

- Is a diagnostic and therapeutic medical emergency
- Occurs in middle-aged patients with no immunocompetent history
  - HSV2 in young patients 20–30 years
  - HSV1 and HZV patients 50–60 years
- Positive diagnosis is difficult
- Acute onset with-red eyes, moderate pain, photophobia, decreased AV
- Initially unilateral, bilateralized in 1/3 of cases, with evolution, 6 weeks to 7 months
- Inflammatory changes in the anterior segment
- Scleritis, episcleritis
- Changes at the rear pole
  - retinal necrosis localized on the periphery of the retina, expanding circumferentially, then centripetal towards the posterior pole
  - peripheral occlusive vasculitis
  - hyalitis
  - papulitis

BARN (bilateral acute retinal necrosis) in 35% in patients with Necrosis acute bilateral d'embly. Exudative DR with reserved prognosis, with numerous retinal ruptures and epiretinian membrane. Bilateral form is a risk factor for encephalitis

- General neuro-ophthalmic signs-meningoencephalitis (requires MRI)**CMV**

Congenital CMV infection

- Ocular
  - peripheral multifocal retinocoroiditis, which in the scarring phase becomes pigmented
  - atrophy of the optic nerve

Acquired CMV infection

- Ocular
  - retinitis with areas of slowly progressing peripheral retinal necrosis progressive or fulminant complicated with AO and DR
  - damage to the anterior segment shows an average uveal inflammation

The condition may be present in immunodepressed children after chemotherapy, kidney transplant, AIDS

- Treatment
  - systemic Ganciclovir, intravitreal Ganciclovir
  - systemic foscarnet, intravitreal
  - systemic cidofovir
- Prognosis
  - Good initial response in 95%, in 50% relapse after 6 months
  - Favoring factors: increased CD4 in antiretroviral therapy.

Parasitic Uveitis

Toxoplasmosis

Parasitic disease caused by Toxoplasma gondii, toxoplasmosis is the most common cause of posterior uveitis 25% in the acquired form and 90% in congenital form.

- Ocular
  - signs of granulomatous anterior uveitis with retrocorneal precipitates, intraocular hypertension or not
  - chorioretinitis with whitish foci localized in the vicinity of scars pigmented (satellite lesions)

  - recurrence of toxoplasmic infection is suspected in the presence of satellite lesions
  - juxtapillary particular localization with Jensen chorioretinitis (sometimes)
  - atypical appearance in AIDS (HIV is suspected in extensive bilateral forms)
- Eye complications
  - damage to the macula, papillo-macular fascia, damage to the papilla or great vessels
  - indirect damage to the macula by retinal detachment, fibrosis
- Treatment (Table 11.8)
  - in immunodepressed patients it will be done in all lesions
  - in immunocompetent patients in:

    lesions of the macula, papillo-macular bundle, large vessels
    severe hyalitis

General corticotherapy—never administered on its own, administered 48 h after the establishment of antitoxoplasmic treatment.

- Laser photocoagulation for neovascularization
- Vitrectomy—if needed

Toxocarosis

- Parasitic disease caused by Toxocara canis or Toxocara catis affects more often children 2–9 years old, who consume unwashed plant foods infested with parasite eggs
- Ocular
  - posterior pole granuloma which, if not complicated, may remain undetected

Table 11.8 Antitoxoplasmic treatment

Medication	Dose	Duration	Side effects
Sulfadiazine (adiazine)	100 mg/kg/day 4 doses 6 weeks No more than 4000 mg/day = 8–12 tablets/day in 3 rounds	6 weeks	• Renal lithiasis • Allergic reactions • Stevens–Johnson syndrome
Pyrimethamine (malocide, daraprim) 1 day	• 50 mg/2 tablets/day • 25 mg->1 cp/day Associated with folic acid	One day, 4–6 weeks	• Thrombocytopenia • Leukopenia • Folate deficiency Control—weekly blood count
Clindamycin (dalacin)	300 mg 4 times/day	3 weeks	Pseudomembranous colitis
Cotrimazole (bactrin)	4 cp/day in 2–3 rounds, single or associated with clindamicin	4–6 weeks	
Atovaquone	750 mg 3 times/day		
Azithromycin	500 mg/day	3 days	

  - peripheral granuloma
  - severe chronic endophthalmitis with total loss of vision, leukocoria, strabic deviation

- General: fever, adenopathy, hepatomegaly, eosinophilia, pneumonia.
- Treatment
  - Antiparasitic drugs thiabendazole, Albendazole, Ivermectin-no are effective for eye injury, or may cause increased inflammation secondary to the destruction of the parasite
  - Corticosteroids-systemic and periocular
  - Vitrectomy in: endophthalmitis, traction with retinal detachment

Pneumocystis carinii—Opportunistic infection, major cause of mortality and morbidity in AIDS

Onchocercosis
- Infection with Oncocerca volvulus, filaria transmitted by fly sting black
- Ocular
  - anterior uveitis with papillary distortion
  - chorioretinitis with damage to the pigment epithelium and chorioretinian allergy
  - KPS
- Treatment: Ivermectin

Fungal Uveitis

Ocular Histoplasmosis

- Fungal infection with Histoplasma capsulatum, in 95% asymptomatic, localized frequently to the choroid where it remains dormant, from where it can reactivate
- Ocular
  - peripapillary atrophy and in the middle periphery of the posterior pole
  - exudative maculopathy with its consequences NVC
- Treatment
  - argon NVC laser photocoagulation (AFG detected)
  - vitrectomy

Candida albicans

- Candida infection occurs in intravenous drug addicts or catheter carrier patients
- Eyepiece
  - anterior uveitis + hypopion (rare)
  - multifocal chorioretinitis
  - cotonous vitreous nodules
  - chronic endophthalmitis
- Treatment
  - Oral fluconazole
  - Amphotericin B intravitreal in endophthalmitis
  - Vitrectomy when needed

Intraocular Mycoses

- Intraocular Mycoses are serious but rare conditions in which the germ penetrate the eye on the way:
  - Exogenous by accidental introduction of fungi into the eye after interventions ocular surgery, perforated trauma (with vegetal, Earth), perforated comean ulcer.
  - Endogenous-by fungal septicemia in fungal endophthalmia in people with a particular land, commonly infected with Candida, Aspergillus, Cryptococcus (rare)
  - Approximately 10% of patients with candidemia develop endophthalmitis
  - Candida albicans is common in the general population 70% in the tubule digestive oral cavity, urogenital sphere
  - Endogenous endophthalmitis with candida can be isolated Candida infection albicans or other species: *C. parapsilasis*, *tropicalis*, *C. stelatoidea*.
- It is necessary to establish an early diagnosis of possible infection with candida and systemic antifungal prophylaxis to limit the serious development of treatment of candidiasis endophthalmitis
- Systemic—concomitant touching of several organs:
  - endocarditis
  - pneumopathies
  - nodular or pustular skin lesions
  - osteoarticular determinations
- Ocular
  - Symptoms

    at the onset; minimal AV decrease, mobile flies
    visual acuity decreases brutally when chorioretinal foci appear

- Clinical signs

  variables depending on the location, extent and severity of lesions
  creamy white chorioretinal foci, accompanied by inflammatory damage to vitreous (with abscess in the vitreous and subretinal abscess), anterior segment with uveitis, with synechia and hypopion
  Periphlebitis
  infectious foci are initially isolated and localized in the posterior pole, but they quickly become multifocal
  retino vitreous haemorrhages
  after resolution foci leave pigmented scars
  epimacular membrane
  vitreo-macular traction syndrome
  macular hole
  choroidal neovascularization
  DR

- Curative treatment of candida infection is general, on a long time, administered intravenously:
  - Amphotericin B (low intraocular penetrance)
  - Fluconazole-oral, but Spectrum is lower
  - Voriconazole
- Surgical treatment-vitrectomy
- Intravitreal injection of voriconazole or amphotericin B
- The prognosis of fungal lesions is reserved

Mycobacterial Uveitis

Tuberculosis

- Chronic granulomatous infection caused by bovine tubercle bacillus (***Mycobacterium bovis***) or human (***Mycobacterium tuberculosis***)
- **The most common form of ocular tuberculosis is uveitis granulomatous, eye damage secondary to a primary focus**
- Ocular
  - granulomatous anterior uveitis (common),
  - negranulomatous
  - posterior uveitis with focal choroiditis, multifocal, hyalitis, Dalen nodules Fuchs 30–50%
  - Localised serous DR, papillary oedema, retinal periphlebitis
  - isolated choroidal granuloma
  - panuveitis
  - flictenular keratoconjunctivitis, interstitial keratitis

- General
  - tuberculosis can affect any organ
  - fever, weight loss, night sweats, prolonged subfebrility
  - fibrocaseous lung disease
- Treatment
  - Isoniazid-150 mg/day
  - Pyrazinamide-2 g/day
  - Rifampicin-600–900 mg/day
  - Ethambutol for 12 months

Spirochete Uveitis [32]

Syphilis

- Sexually transmitted Treponema pallidum infection
- Congenital
  - parenchymal keratitis
  - posterior uveitis
  - bilateral syphilitic chorioretinitis with "salt and pepper" appearance
- Acquired
- Ocular
  - acute, bilateral anterior uveitis in 50% in secondary syphilis, which can be associated with dilatations of Irian—roseola capillaries and/or Irian atrophy post-inflammatory
  - posterior uveitis with focal, multifocal chorioretinitis
  - optic neuropathy
  - panuveitis
  - oculo-motor paralysis
- Treatment
  - Penicillin G—12–24 million IU/day
  - Extencilin 2.4 UM-I. m/day associated with oral probenecid 2 g/day, 10–15 days
  - Amoxicillin oral-3 g 2/day-28 days

Lyme Disease [33]

Is a systemic disease caused by the spirochete Borrelia burgdorferi transmitted by sting of Ixodes spp. with dermatological, articular manifestations, neurological and ophthalmologic stages.

- Ocular
  - granulomatous anterior uveitis
  - intermediate uveitis
  - retinal vasculitis
  - peripheral multifocal choroiditis
  - neuroretinitis
  - oculomotor paralysis
  - periorbital oedema
  - orbital myositis
  - conjunctivitis
  - keratitis
- General
  - stage evolution
  - chronic migratory cutaneous erythema (pathognomonic), adenopathy, meningitis, myocarditis
  - late-chronic arthritis of large joints, polyneuropathy,
- Treatment—Doxicillin-oral 100 mg 2/day, 3 weeks

BRUCELLA—uveitis in endemic areas
LEPTOSPIRA

Specific Uveitis

Heterochromic Uveitis-FUCHS (UHF)

- Unilateral disease with chronic course, without functional signs, having a asymptomatic anterior uveitis at onset, discovered by chance, present in the young adult with secondary cataract and difference in coloration between the iris the two eyes Irian heterochromia.
- Ocular
  - discrete anterior uveitis with small precipitates on the endothelium, filaments and fibrin
  - diffuse stromal atrophy with Irian nodules on the border of the pupil
  - Irian heterochromia with cataracts on the hyperchromic eye
  - hyalitis
  - Amsler sign after puncture as in cataract surgery a hemorrhage occurs angled
- Complications
  - Cataract
  - Slow-developing glaucoma

- Treatment
  - corticotherapy is ineffective
  - mydriatics are not needed
  - extraction of the lens with great caution, sometimes filter operation

Posner-Schlossmann Syndrome

- Affects the young man more frequently, with the disease developing in pusee recurrent, white-eyed, painless (or very slightly painful) unilateral
- Ocular
  - acute, recurrent, unilateral uveitis
  - ocular hypertonia, medium that may precede inflammatory signs
  - epithelial corneal edema, related to the HIO crisis
  - Tyndall effect after which occur:

    centrally whitish precipitates, surrounded by small satellite precipitates
    never the Irian synechi
    iris and pupil normal
    open iridocorneal angle
    there are no posterior eye injuries

Cataract-Induced Uveitis

- Crystalline-induced uveitis called phacoantigenic, phacoanaphylactic uveitis or facotoxic is produced by mobile crystalline fragments in CA or/and in the vitreous.
- Acute or chronic intraocular inflammation, anterior and rarely posterior is reactive to crystalline proteins
- The presence of free crystalline fragments come from:
- Surgery for cataracts, uveitis being more common after
  - Phacoemulsification surgery even rarer after extracapsular extraction
  - Dislocation of crystalline fragments in the vitreous
  - Opening of the anterior capsule after trauma or other interventions intraocular surgery
  - Hypermature cataract, in which the lens capsule becomes permeable
- Treatment
  - has the major objective of removing crystalline debris responsible for inflammation
  - small, medium inflammation

- local corticotherapy or peribulbar injections to reduce acute episode
- lens extraction
  - severe inflammation, lack of response to corticotherapy, refractory HTIO or residual fragments require-vitrectomy
  - if HTIO persists-surgical treatment multifocal idiopathic uveitis with white spots

Multifocal Idiopathic Uveitis With White Spots

Multiple Evanescent White Spot Syndrome-Mewds

- Unilateral, self-limited pathology with favorable prognosis, more common in young women 20–30 years with decreased vision and photopsies
- Clinical [7]
  - moderate inflammation of the CA and vitreous
  - FO examination shows: rare vitreous cellular Tyndal, white spots, small, round, predominate in the posterior pole and around the optic nerve extending to in the middle and retroequatorial periphery where they have smaller dimensions, located in the EP or in the external retina white spots may surround the fovea which has a reddish granite appearance
  - papillary oedema
- Evolution towards spontaneous resolution with residual alterations in EP and persistence macular granite appearance
  - Good prognosis, rarely small chorioretinal scars

Epitheliopathy in EPP or APMPPE Plaques

APMPE—acute posterior multifocal placoid pigment epitheliopathy is a bilateral self-limiting disorder commonly associated with HLA B7 and HLA-DR2 with good prognosis, with onset 30–50 years and variable symptoms depending on the localization spots.

- Retroequatorial and in the posterior pole, multiple retinal lesions white, yellowish, subretinal in relatively discrete plates, sometimes confluent in the posterior pole
- Evolution: spontaneous healing in a few weeks with residual depigmentation of EPR
- Etiology—unknown, incriminate lyme, streptococcal infection, viral, allergy on ampicillin, sulfonamides, after hepatitis B vaccination

Serpiginous Choroiditis

- Rare, relapsing, bilateral progressive inflammatory disease that affects the choroid and EP, with reserved prognosis.
- It is a strictly ocular disease, without systemic manifestations,
- Ocular
  - discrete anterior uveitis with hyalitis
  - subretinal infiltrates with blurred edges, debuting around papilla and progressively expand into the Serpentine
  - proliferation of choroid neovas
  - atrophic cicatricial lesions with edema of the macular retina

Prognosis reserved by macular atrophic scars and dense scotomas with AV decrease.

Treatment
- Corticotherapy
- oral, IV, peri, intraocular
- high dose effective
- Immunosuppressants—cyclosporin, azathioprin, cyclophosphamide, chlorambucil
- Laser photocoagulation or PDT for neovascularization
- antiangiogenic agents are effective

Idiopathic Multifocal Choroiditis

- Is the same as multifocal choroiditis with CMP panuveitis and choroiditis dotted-internal ICC (not unanimous consensus)
- Idiopathic choroidal inflammatory disease in young adults, women who may had medium myopia with potential for unilateral, bilateral neovascularization simultaneously or successively
- Clinical signs
  - Moderate negranulomatous anterior uveitis
  - Discrete, moderate hyalitis

CMP-Multifocal Choroiditis with Panuveitis

- Small deep yellowish spots at the level of EP in the middle periphery, inferonasal, solitary or very numerous lesions, sometimes common, concentric papilla
- Inactive lesions with net and pigmented edges

CPI-Internal Punctate Choroiditis

- Bilateral lesions in EPR and choriocapillary with estromped edges, sometimes clustered
- Well delineated scars after a few weeks
- Complications
  - foveal scar
  - choroidal neovascularization

Treatment
- Corticoids
- Immunomodulators
- Laser treatment
- Intravitrean antiangiogenic

Retinocoroiditis Birdshot-BRC

- Is a rare form of Intraocular Inflammation with a reserved prognosis, chronic, bilateral.
- Clinically manifested by…
  - posterior uveitis with characteristic chorioretinal lesions of "white spots". creamy-looking and pigmented areas with painless white eyes of varying degree symptoms of visual dysfunction (myodesopsia, nictalopia, photophobia, visual impairment colors)
  - anterior uveitis and discrete hyalitis
- Complications: Cystoid macular oedema, neovascular membrane, oedema of NO early, optic atrophy, intravitreal haemorrhage, subretinal fibrosis, OVCR, ram, macular hole, DR, DRR.

Aggressive Treatment
- Corticotherapy-periocular, oral, I. v., in a timely manner can be beneficial with:
- Prednisone 1–1.2 mg/kg/day orally
- Methylprednisone IV infusion 500–1000 mg/day-3 days, followed by oral cortisone, whose posology slowly diminishes over time
- Corticodependence (usually at doses >20 mg/day requires the use of treatment with immunomodulators
- Intravitreal corticotherapy in combination with immunomodulator
- Corticoids are useful for controlling acute outbreaks
- Symptomatic treatment
  - laser photocoagulation of the retina in ischemia with neovascularization
  - intravitreal injection of growth factor inhibiting agent antifouling in case of choroidal neovascularization

  - vitrectomy for ablation of the epithetine membrane

- Continuous OCT surveillance, clinic, Amsler test, CV, OCT
- Immunosuppressants—Cyclosporine A
  - limited for nephrotoxic side effect
  - 2.5–5 mg/kg/day with creatinine surveillance
- Azathioprin 1.5–2 mg/kg/day associated with cyclosporine could control eye inflammatory process
- Cyclophosphamide
- Chlorambucil
- Mofetil mycophenolate
- IL-2 antireceptor monoclonal antibodies and T lymphocytes
  - TNFa (tumor necrosis factor)
  - Daclizumab

Masked Syndromes-Pseudouveitis

- Masked syndromes or "pseudouveitis" are a variable group of diseases in the most tumours that can mimic an intraocular infectious-inflammatory condition
- the causes of masked syndrome are malignant or non-malignant, but have a common feature-**uveal intraocular inflammation does not occur by immune mechanism**
- **uveitis in masked syndrome is secondary non-inflammatory, anterior, intermediate, posterior** [20, 34]
- Etiology of masked syndrome [35]
  - tumorous disorders
  - retinoblastoma
  - leukemia-acute, chronic
  - lymphoma
  - metastases from adenocarcinoma
  - juvenile xanthogranuloma
- Uveitis related to Drug Administration: rifabutin, cidofovir, sulfonamides, triamcinolone, systemic corticoids
- **Uveitis in ischemic syndrome of the anterior segment**
  - atheromatous carotid stenosis
  - Takayaso arteritis
  - Horton's arteritis
- Other non-malignant causes that can produce masked syndrome: foreign body in anterior chamber, Dr regmatogenic, myopic degeneration, syndrome pigment dispersion, retinitis pigmentosa, multiple sclerosis, postvaccinal reaction.

- Neoplastic conditions that can give pseudouveitis: acute lymphoid leukemia, chronic, chronic myeloid leukaemia, T cell lymphoma/leukaemia of adult, familial amyloidosis, primary CNS lymphoma, intraocular lymphoma primary, paraneoplastic syndrome, Vogt Koyanagi Harada, retinoblastoma.**Masked syndrome with anterior segment damage**

The most common causes of anterior uveitis in masked syndrome are tumor diseases and toxic action of some drugs.

Tumor Diseases

Retinoblastoma

Retinoblastoma is an embryonic malignant tumor of ectodermal origin which is present in the young child.

Classical RB is clinically manifested by: leukocoria, strabismus, decreased AV.

Diagnosis of masked syndrome in RB is difficult because the manifestation of anterior uveitis can be variable by…

- diffuse retinoblastoma with anterior infiltration and extension
- conjunctival hyperemia and pseudohypopion

Treatment of uveitis is ineffective.

Clinical examination completed with Oct ultrasonography, CT, MRI correct positive diagnosis.

***Leukemia*—Acute lymphoblastic leukemia** present in a child or young adult can produce ocular determinations during periods of relapse (exceptional at onset).

- Masked syndrome is manifested by…
  - bilateral cellular hypopion
  - isolated uveitis or accompanied by hematological relapse
  - the diagnosis is confirmed by identifying tumor cells in watery humor after puncture of the anterior chamber
  - **Chronic lymphoblastic leukemia** in older people is manifested by anterior uveitis.

Periocular Lymphoma

- Periocular lymphoma includes: Hodgkin's lymphoma, Burkitt's lymphoma, other lymphomas malt-associated lymphoma with mucosal starting point-intestinal, primary conjunctival (B-cell) lymphoma.

Pseudouveitis by Non-tumor Diseases

Anterior Pole Ischemic Syndrome

It is produced by complete atheromatous occlusion of the internal carotid artery at elderly people or by inflammatory arteritis in adults, in Takayasu arteritis, Horton's arteritis.

Eye inflammation given by drugs

Pseudouveitis during treatment with **rifabutin** (antiTBC is manifested by…

- anterior uveitis with serofibrinous exudate and hypopion, rarely with determinations to rear pole level
- uveitis disappears with discontinuation of treatment and local corticoids

Cidofovir—is an antiviral used in cytomegalovirus eye infection which can generate…

- asymptomatic torpid anterior uveitis associated with iris atrophy and ciliary body
- pupillary seclusion and eyeball atrophy

Bisphosphonate—can give anterior uveitis, episcleritis, scleritis

Triamcinolone intravitrean can give an intravitrean inflammatory process "pseudoendophthalmitis", **which, however, quickly succumb**

- **Masked syndrome with damage to the posterior pole** Pseudouveitis with posterior determinations most commonly are of cause tumor, the main cause of which is ***primitive intraocular lymphoma LIOP*** (rare) whose incidence has increased over the past 20 years manifested by…
  - intermediate uveitis with, without, "ant eggs"
  - hypopion

Eye inflammation may initially be sensitive to corticotherapy, but over time inflammation worsens under corticotherapy.

LIOP Treatment

- depends on the age of the patient and the presence or not of cerebral tumor localization
- the most effective treatment for primary CNS LIOP/lymphoma is methotrexate
- adjuvant treatment
  - Rituximab (mabtera)
  - Radiation therapy with possible side effects especially in people in age**Eye damage in Hodkin lymphoma and systemic non-Hodkin**

Hodkin's disease can be complicated by secondary lymphomatous neoplastic infiltration at the choroid level.

Paraneoplastic Syndromes

- Retinopathy associated with small cell lung carcinoma-CAR
- Retinopathy associated with malignant melanoma-MAR

Other causes that can produce pseudouveitis

- Multiple sclerosis
  - Periphlebitis
  - Pars planitis-optic neuritis
- Juvenile xanthogranuloma
  - Small Irian tumors
  - Reaction of the previous chamber
  - Spontaneous hyphema.

Purulent Uveitis

- Are inflammation of the uveal tract by pyogenic bacteria aureus, Streptococcus, Pseudomonas, pneumococcus, Staphylococcus epidermidis, Corynebacterium, Propioni acnes, Actinomices.
- **Rarely, purulent uveitis can be produced by fungal infections: Fusarium, Candida.**

Endophthalmitis

- Are serious eye diseases (infectious, rarely non-infectious), affecting ocular contents, aqueous humor and vitreous body.
- Etiologically, endophthalmitis is…
  - **Infectious endophthalmitis** (most serious)
  - Exogenous-is purulent inflammation produced by exogenous infection after perforating lesions, in: perforating corneal ulcer, postoperative, PTSD.
  - Endogenous or metastatic in septicemias, serious outbreak infections.
  - Secondary-by extension of a purulent inflammation from cellulitis orbit, thrombophlebitis, corneal ulcer.
- **Non-infectious sterile endophthalmitis**
  - Postoperative-toxic reaction to IOL, instrumentation
  - Posttraumatic
  - Intraocular Tumors
  - Phacoanaphylactic—by crystalline proteins in morgagnian cataracts
- Clinical Aspects in endophthalmitis
  - Acute bacterial postoperative endophthalmitis
  - Rapid onset under 1 week

  - Is the most serious complication of intraoperative surgery in which the source of infection is the periocular bacterial flora in the eyelid, conjunctiva, lacrimal sac, instruments, staff, etc.

- Symptoms
  - severe eye pain
  - redness
  - lacrimation
  - photophobia
  - significant decrease in vision
- Clinical signs
  - red, purple eye oedema
  - conjunctival chemosis with important conjunctival congestion
  - corneal edema ± corneal infiltrates
  - hypopion in CA
  - Iris if visible, it is edematous
  - the pupil shows a yellowish reflex given by purulent exudation from the vitreous
  - exudation in the vitreous, sometimes yellowish-white mass localized in the fixed pupil in mydriasis
  - increased early TIO in severe cases
  - FO can not be examined

Subacute endophthalmitis—Onset between 1–4 weeks
Chronic endophthalmitis—Clinical manifestation after 4 weeks.
Clinical forms

Exogenous Endophthalmitis

Postoperative endophthalmitis sets in after surgery penetrating: cataract, keratoplasty, vitrectomy.

Acute Postoperative Endophthalmitis [36] (Fig. 11.4)

- Onset under 6 weeks.
- Generated by Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus viridans, gram (−), pseudomonas type, Haemophilus.
- Risk factors: blepharitis, iris prolapse, vitreous, contamination 10 L, diabetes, chronic alcoholism
  - after cataract surgery IOL—Staphylococcus epidermidis, aureus, Pseudomonas

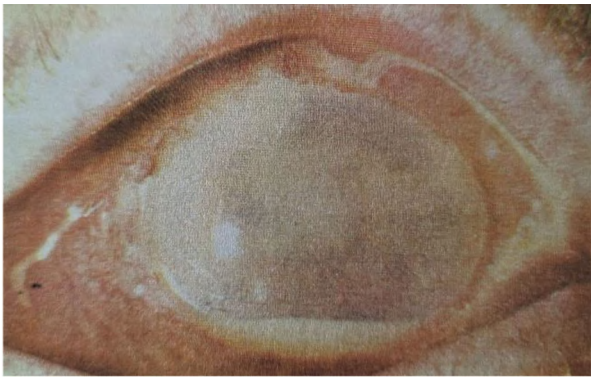

Fig. 11.4 Postoperative bacterial exogenous endophthalmitis

  - after filter surgery-Streptococcus, Haemophilus

- Treatment-intravitreal Antibiotic: vancomycin, amikacin, dexamethasone.

Chronic Postoperative Endophthalmitis

- Onset 6 (six) weeks after surgery.
- It is produced by propionibacterium acnes, coagulase-negative Staphylococcus, fungi.
- Long Course (months) with chronic granulomatous inflammation white/gray in the capsular sac.
- Treatment
  - antibiotic in the vitreous and capsular sac
  - vitrectomy in pars plana with vancomycin intravitreal administration (and in capsular sac).

Endophthalmitis Associated with the Filtration Bubble

- Clinical appearance with acute onset, associated with the presence of filtration bubble, and severe intraocular inflammation with hypopion, several months postoperatively.
- Initial infection may be at the level of the filter bubble with extension to CA and vitreous (Haemophilus species present in this type of endophthalmitis are very virulent).
- Treatment
  - immediately supported
  - intravitreal antibiotic
  - vitrectomy.

Post-traumatic endophthalmitis occurs after penetrating eye trauma, by contaminating the eye contents with external germs.

Bacterial Endophthalmitis

- Onset by variable inflammation with Staphylococcus, Bacillus germs ceres 25% (which should be identified by culture and antibiogram)
- Treatment
  - emergency
  - antibiotic after antibiogram (topical subconjunctival, systemic, intravitreal)

Mycotic Endophthalmitis

- Has indolorous evolution
- Onset days, weeks after trauma with plant bodies or objects contaminated with soil.

Endogenous Endophthalmitis

- 2–8% of all endophthalmitis
- Results from haematogenic dissemination, in a septicaemia, under conditions favoring (leukemia, AIDS, diabetes, cirrhosis, etc.).

Bacterial Endophthalmitis

- Positive diagnosis is given by CA paracentesis, vitrectomy, with sampling of AU, vitreous body, cultures and antibiogram (sometimes sterile cultures)
- Treatment: vitrectomy, immediate topical antibiotic, oral, intravenous, periocular, intravitrean
  - intravitrean-vancomycin for Gram (+), amikacin for Gram (−), ceftazidim for Gram (−), clindamycin for Bacillus
  - intravenously—vancomycin, amikacin, ceftazidim
  - periocular
  - topically-fortified antibiotics, cycloplegics, steroids, vitrectomy.

Endogenous Metastatic, Bacterial, Fungal Endophthalmitis

- Rare condition in immunologically impaired patients, malnourished children
- Treatment: appropriate antibiotic, vitrectomy

Fungal endophthalmitis: Candida, Aspergillus, Cryptococcus, Coccidioidomycosis
Prophylaxis of endophthalmitis

- Identification and treatment of risk factors: transplantation, cancer, diabetes, AIDS
- Prophylaxis of postoperative endophthalmitis
  - treatment of blepharitis, postponing the operation if necessary
  - betadin preoperative 2 min
  - topical antibiotic in hours, days before surgery: vancomycin, amikacin
  - doxicillin for rosacea, seborrheic dermatitis
  - sterile adhesive fields
  - sealed incisions
  - Antibiotic

    subconjunctival: vancomycin, Amikacin
    intracameral Antibiotic-questionable (irrigation solution)
    if needed systemic + intravitreal treatment (no superior results): Vancomycin, Ceftazidime, Amikacin
    Oral

    fluoquinolone
    caution when removing wires, requires disinfection with pavidon 5%
    corneal protection with doxicillin (could be useful in inflammation of the filtration) and vitamin C, a powerful proinflammatory cytokine inhibitor.

- The prognosis of endophthalmitis (it is reserved in the endogenous form) depends on germ virulence, patient, AV value at Presentation.
- The progression of endophthalmitis towards improvement is slow, but the decrease in pain and edema of the eyelids may be signs of a favorable course, correlated with repeated ultrasonography.

Treatment of endophthalmitis—should be carefully supervised, be established immediately and be adapted to the clinical form.

Antibiotic treatment in endophthalmitis is:

- **Intravitreal:** vancomycin, ceftazidime, amikacin, gentamicin
  - addition of dexamethasone 0.4 ml in 0.1 ml to limit the consequences postinflammatory
  - vitreous fluid suction for bacterial cultures
  - repeat the injection after 48 h, depending on the antibiogram

- **SUBCONJUNCTIVAL** 5–7 days to maintain a concentration intraocular therapy: vancomycin, ceftazidime, cefuroxime.
- **Topical ANTIBIOTIC**-at 30′, 1 h: vancomicim, ceftazolin, amikacin or tobramycin.
- **Systemic ANTIBIOTIC**-oral, intravenous: ciprofloxacin, vancomycin, ceftazidime, cefazolin or amikacin.

Steroid treatment limits the inflammatory process it is indicated to be used 24–48 h after initiation of treatment antibiotic (other authors recommend immediate treatment)

- intravitrean = dexamethasone 0.4 mg/0.1 ml
- subconjunctival = dexamethasone 4 mg/1 ml = 5–7 days
- topical = dexamethasone 0.1%
- systemic-oral after 24 h of antibiotic, 60 mg prednisone, low 10 mg, 2 (two) days for each dose.

Combination Treatment

- Cycloplegic-atropine 1%
- Antiglaucomatous medication as needed
  - timolol 0.5–1%
  - acetazolamide 250 mg 3/day
- Vitrectomy indicated in patients undergoing intensive treatment 48–72 h severe infection does not improve and AV reduces to perception of light.

Panophthalmia

- Is purulent inflammation of the eyeball in its entirety, including the capsule Tennon.
- The starting point may be anterior, posterior or purulent uveitis both, after a reduced stage of endophthalmia.
- It is an acute bacterial infection by germs that cause endophthalmia.
- Symptoms
  - eye pain and intense headache
  - complete loss of vision
  - intense tearing
  - purulent discharge
  - red eyes
  - impaired general condition with fever

- Clinical signs
  - palpebral oedema marked violet red
  - limited and painful eye movements
  - conjunctival chemosis, with perikeratic conjunctival hyperemia, violet red
  - corneal edema
  - hypopion in CA
  - completely lost vision, even loss of light perception
  - sometimes punctured globe to the limb
- Complications
  - orbital cellulite
  - Cavernous sinus Thrombosis
  - meningitis, encephalitis
- Treatment
  - Analgesics and anti-inflammatories to reduce pain
  - Antibiotics for neighborhood structures
  - Gutting.

Treatment in Uveitis [37]

Infectious inflammatory uveal pathology requires adequate treatment for preservation of visual function. Local and/or systemic corticotherapy is effective, but its use time long term it can be associated with serious eye complications—cataracts and glaucoma or eye superinfection, sometimes systemic complications are also possible.

In uveitis it is necessary to quickly institute appropriate treatment depending on etiology, clinical appearance and course of the disease, to exclude relapse and to limit complications in severe forms of uveitis.

Clinical examination establishes the type of anterior, intermediate uveal inflammation, posterior, total and depending on this the therapeutic attitude is differentiated after localization in the uvea of the inflammatory infectious process and after the course of the disease in the course of the evolution of a localized uveitis, a process can occur inflammatory neighborhood and then the therapeutic attitude will be adapted in a clinical context. The goals of treatment in uveitis are…

- preservation or recovery of visual function
- elimination (limitation) of uveal inflammation
- fighting eye complications
- therapeutic control of the disease

Depending on the clinical form and course **treatment in uveitis** is…

- **Etiological treatment**
- **Symptomatic treatment**
- **medical**
  - **local**
  - **general**
- **surgical**

Medical Treatment

Local Treatment

- Topical
  - Mydriatic, cycloplegic
  - nonsteroidal anti-inflammatory drugs-NSAIDs
  - anti-inflammatory corticosteroids—drop solution, at a rate of administration at 15′, at an hour, 3, 5, 7 times a day ointment at bedtime
- Injections
  - subconjunctival, latero, retrobulbar with antibiotics, injectible cortisone solution
  - Intraocular—in the anterior chamber-antibiotic
- intravitrean-cortisone, antibiotic, anti VEGF

General Treatment

- NSAIDs
- corticosteroids
- antibiotics
- immunosuppressants
- immunomodulators

Surgical Treatment-Cataract, Glaucoma—it is done only at the time of extinguishing the acute spurt, on the quiet eye, under antibiotic control

Treatment of complications

Local Treatment

Mydriatic and Cycloplegic (Table 11.9)

- Midriatics and cycloplegics associated with non-steroidal anti-inflammatory drugs local topical is the initial local treatment in an anterior uveitis
- Objectives of mydriatic and cycloplegic treatment
  - prevents and prevents the formation of posterior synechiae or produces breaking old synechia
  - promotes the reduction of inflammation through the decongestion of the iris and body ciliary, by mydriasis and cycloplegia and decreases vascular permeability with reduction of inflammation and exudation
  - limits the complication with cataracts and macular edema
  - soothes pain
  - avoids accommodative spasm

Rate of administration of mydriatics and cycloplegics associated with anti-inflammatory drugs used in the topical treatment of anterior uveitis, depend on nature, severity, course of uveitis

- During the day mydriatics and cycloplegics are administered topically, ocular, in the form of drops, at the rate of administration depending on the form symptoms of uveitis: by the hour, 3–5 times a day, and in the evening in the form of ointment
  - In hyperacute uveitis HLA-B27 Mydriatic one drop can be applied to 15 min paired with colir with dexamethasone 0.1% or prednisolone 1%.
  - Long-acting mydriatics are initially used and for maintaining mydriasis then short-lived cycloplegics can be used that allow pupil to remain mobile to prevent the formation of synechia hindquarters
- short-acting mydriatics will also be used to avoid formation peripheral synechia if a long-lasting Mydriatic is used action
- the duration of administration should be extended to strengthen the process healing and limitation of relapses

Table 11.9 Mydriatic and cycloplegic effect

	Mydriasis		Cycloplegic	
	Maximum (min)	Recovery	Maximum (min)	Recovery
Atropine	30–40	7–10 days	1–3	7–12
Homatropine	20–30	5–7	0.5–1	5–7
Scopolamine	40–60	1–3	0.5–1	1–3
Cyclopentolate	30–60	1	0.5–1	1
Tropicamide	20–40	0.25–1	0.5	<0.25
Phenylephrine	20–60	3–6		

Parasympathetic

Atropine sol. 0.5–1%, ointment 0.5%
- Mydriatic and cycloplegic with prolonged action 6–8 days in the form of sulfate of atropine 0.5–1% cholir and ointment in the infant, toddler administering atropine carefully, 1 drop 0.5% with lacrimal point compression because it can give intoxication
- is indicated in anterior plastic uveitis, associated with spondylarthropathies
- side effects
  - ocular: eye irritation, glaucoma attack in GPUI, increased TIO in GPUD
  - general: dry mouth, urine retention, drowsiness, convulsions, mental confusion, respiratory depression
  - contraindications: atrial fibrillation, urine retention

Homatropin
- as homatropin hydrobromic concentration 1%
- long cycloplegic effect
- maximum Mydriatic effect at 40 min, maximum Mydriatic effect lasts 20 h, return to normal pupil in 1–3 days
- indicated in the treatment of uveitis 1–2 drops every 3–4 h

Scopolamine-0.25%
- shorter duration of action but longer mydriasis than atropine
- cycloplegia of short duration
- more important neurological toxicity in older people
- side effects-the same as with atropine, but of shorter duration

Cyclopentolate-0.5–1%, 1 drop, repeated
- synthetic drug used in the form of collir 0.5–1% with very good cycloplegic effect, in the form of 0.5–1 collir%
- indicated in people hypersensitive to atropine

Sympathomimetics

Neosinephrine-Phenylephrine
- synthetic sympathomimetic with Mydriatic effect without cycloplegic effect
- collar 5–10–15%
- side effects: palpitations, headache, HTA
- administered with caution to cardiac, elderly.**Therapeutic indications of mydriatics, cycloplegics**

Atropine
- 0.5–1% solution, 1 drop of the motherwort 2–4/day 0.5%—in children

- treatment of uveal inflammation in anterior, intermediate uveitis or in uveal reaction secondary to an aggression or after surgical treatment
- cycloplegia for refraction, particularly in accommodative strabismus
- to achieve optical penalty in the treatment of unilateral amblyopia

Homatropine Hydrobromide
- 1% solution, 1 drop 2–4/day
- treatment in keratitis, uveitis, scleritis, episcleritis
- optical penalty in amblyopia

Cyclopentolate
- 0.5%—1 drop to child 1–3 years, 2 drops to child >3 years
- Refractive measurement
- Preoperative mydriasis for cataracts, photocoagulation

Midriaticum
- Tropicamide-0.5%
- Therapeutic or diagnostic mydriasis

Neosinephrine
- Phenylephrine Hydrochloride 10%, 1–3 instillations
- Diagnosed, therapeutic, preoperative mydriasis

Nonsteroidal Anti-inflammatory Drugs-NSAIDs

Inflammation occurs in the presence of prostaglandins (acid metabolites arachidonic) that generate changes in the hematoocular barrier with increasing vascular permeability

- **Reducing inflammation** can be achieved by…
  - **treatment with non-steroidal anti-inflammatory drugs NSAIDs**
  - **treatment with steroidal anti-inflammatory drugs with immunosuppressive non-specific effect**
  - **specific immunosuppressive treatment** with selective agents used in organ **transplant, immune diseases, cancer**
  - **antihistamine treatment**

Non-selective NSAIDs reversibly inhibit cyclooxygenase 1, 2 with diffuse decrease in synthesis of circulating prostaglandins and thromboxanes, so they reduce the inflammatory process.

- NSAIDs with anti-inflammatory action are prescribed for topical treatment and/or systemic alone or in combination with corticosteroids in:
  - low intensity anterior uveal inflammation of first intention
  - Topical NSAIDs are useful in the treatment of trenant, Recurrent Uveitis, scleritis, macular edema, as long-term therapy

  - Topical NSAIDs in combination with topical steroids, reduce the duration of corticosteroid therapy
  - if NSAIDs are administered for a long time, the dose should be re-evaluated periodically, average tolerance is 6 weeks
  - leukotriene modulated inflammation is partially controlled by NSAIDS
  - Systemic NSAIDs can be used when steroids are contraindicated
  - Phenylbutazone and oxyphenylbutazone have anti-inflammatory potential (Preferential) in uveitis associated with rheumatic diseases

- **Scleritis is the major indication for systemic NSAIDs**
- Contraindications to taking NSAIDs
  - gastrointestinal ulcer
  - recent digestive haemorrhage
- **Systemic NSAIDs**
  - Aspirin-acetyl salicylic acid

    300 mg/day—antiplatelet effect
    300–2400 mg/day—antipyretic, analgesic effect
    2400–4000 mg/day—anti-inflammatory effect
    Ibuprofen, indomethacin 0.5–1 mg/kg/day-analgesic, antipyretic effect with lasting anti-inflammatory potential
    Diclofenac 1 mg/kg/day
    Piroxicam 0.2–0.4 mg/kg/day
    eloxicam 0.15–0.30 mg/kg/day
    Celecoxib 2–4 mg/kg 2/day—is a selective NSAID inhibitor of cyclooxygenase 2

Topical NSAIDs are indicated in…

- different forms of anterior uveitis for their anti-inflammatory effect
- prophylaxis of inflammation before cataract surgery, glaucoma, refractive surgery
- postoperative after cataract surgery, glaucoma
- postfotorefractive after keratectomy
- resolution of Cystoid macular edema after cataract surgery
- treatment of dry eye
  - Indocolir 0.5%
  - Acular–ketorolac 0.4%
  - Ocufen–flurbiprofen 0.03%
  - Nevanac–nepafenac 0.1%
  - Voltaren–diclofenac 0.1%
  - Profenol–supraven 1%
  - Bromfenac-COX2 inhibitor

Corticotherapeutic Treatment

Corticosteroids are drugs used to control inflammation uveal: anterior, intermediate, posterior, being indicated in severe forms of disease, chronic, relapsing

- the effectiveness of corticoids is present in forms of acute uveal inflammation, but there are also some forms of chronic uveitis refractory to steroid treatment
- the anti-inflammatory effect of corticoids is nonspecific, the drug is indicated in multiple uveal etiologies: infections, allergies, trauma

Corticotherapeutic treatment—Corticotherapy in uveitis is used in the form of…

- ***local treatment*** in:
  - ***drop solution*** 3.5/day
  - ***periocular injections***
- ***systemic treatment*** that must be carefully controlled because it can administer in severe uveitis for a long time with possible side effects, corticocorticodependence, corticoresistance

Topical Corticotherapy

- The effectiveness of local corticoid treatment depends on multiple factors:
  - Transcornean penetrating ability
  - Anti-inflammatory action
  - Duration of action in UA, vitreous
  - Dosage and frequency of instillations
- Topical treatment with cortisone in topical administration in droplet solution it is very effective in the treatment of anterior uveitis, for suppression rapid reduction of uveal inflammation, but also to reduce the administration of therapy systemic cortisone, which can generate important side effects (more chosen in prolonged administration)
- Topical treatment is used in combination with cycloplegic and Mydriatic NSAIDs, with hourly administration, with dose reduction if insured control of inflammation.
- Indications of topical corticotherapy in combination with NSAIDs and Mydriatic
  - uncomplicated mild anterior uveitis without or with reduced recurrence (under 1/year)
  - uveitis in ankylosing spondylitis in which the inflammation reduces in 2 weeks with corticotherapy in drops, ointment

Dexamethasone 0.1%
Betamethasone 0.1%
Prednisolone 1%

- middle anterior uveitis

  Fluorometholone 0.1% solution (does not influence the increase in TIO)
  Rimexolone-vexole-1%
  Loteprednol etabonate-lotemax 1%

- In granulomatous uveitis instillations are insufucient, with systemic treatment being necessary.

- Commercial cortisone preparations:
  - Maxidex-solution, ophthalmic ointment-dexamethasone 0.1%
  - Maxitrol-dexamethasone, neomycin, polymyxin
  - Spersadex-dexamethasone, chloramphenicol
  - Tobradex-dexamethasone, tobramycin
  - Ophtameson n-Betamethasone
  - Ophtameson n-Betamethasone, neomycin
  - Betabioptal-Betamethasone, chloramphenicol
  - Garason-Betamethasone, gentamicin
- Cortisone ointments associated with antibiotics
  - Dexamethasone/oxytetracycline
  - Dexamethasone/neomycin/polymyxin B
  - Triamcinolone/neomycin
  - Betamethasone

Corticosteroids: Periocular [38]

- Periocular steroids are indicated in: negranulomatous or granulomatous uveitis that does not respond to topical steroid treatment
- Drugs used in subtenonian or peribulbar injection are:
  - Dexamethasone 4 mg/1 ml ampoules
  - Hydrocortisone 25 mg ampoules 2 ml
  - Methylprednisolone depot-depomedrol = 40–80 mg persists for 6 weeks, but the effect lasts 1 week
  - Administer one ampoule every 2 weeks 4–5 times in succession if not increases TIO
  - Triamcinolone-40 mg subtenon, parabulbar + xyline 2% 0.5 ml.

Intravitreal Corticosteroids [39]

- Intravitreally injected corticosteroids are indicated in the treatment of uveitis severe refractory posterior:
  - EMC after crystalline extraction
  - Exudative DMLV
  - Diabetic maculopathy
- The medicine used is triamcinolone acetonide, kenalog (off label), kenacort with anti-inflammatory, antiangiogenic, antiproliferative effect.
- **Intravitreal Steroid Implants**
  - Fluocinolone Acetonide-retisert 0.5–20 mg with release 2 U/day for 2–3 years, which in non-infectious posterior uveitis decreases recurrence of the disease and improves visual function.
  - Ozurdex-microimplant with dexamethasone 0.7 mg with effect for 5 weeks biodegradable in 50–160 days, with efficacy in uveitis.
  - Iluvien**Corticotherapy in anterior uveitis**

Local corticotherapeutic treatment in the form of colir and ophthalmic ointment it represents the essential treatment in anterior uveitis

- repeated instillations allow to obtain an effective concentration of cortisone in aqueous humor at 5–30′ after instillation
- initially in the anterior uveitis apply instillations of cortisone 1 drop per hour on the first day, then progressively decreasing according to clinical development
- applying the ointment in the evening allows maintaining an eye concentration nocturne

Control of inflammation is given by the regression of the protein and cellular Tyndal effect, which involves progressively decreasing the rate of administration

Treatment should not be continued If eye inflammation is mastered, reasons for the danger of side effects

- After prolonged local treatment with steroids, fungal infections may occur.
- **Acute infections without treatment of infection can be masked by steroids**
- Corticoid in the collir is:
  - excellent treatment in acute anterior uveitis, but it is insufficient in autoimmune uveitis, chronic Recurrent Uveitis
  - no effect on posterior uveitis
  - corticotherapy should be adapted to each case according to the clinical aspect and evolution
  - corticoids should be used with discernment in HSV uveites, never in fungal infections.

Local Corticotherapy in Intermediate, Posterior Uveitis

- Retard corticoid injections are indicated, as they allow an impregnation for therapeutic effect, but with the limitation of side effects systemic effects of steroids
- Intravitreal cortisone injection may be associated with antibiotics in treatment of endophthalmitis

Corticoids with topical administration in combination with antibiotics: Dexamethasone with tobramycin-tobradex 0.1% associated with neomycin, or Neomycin Polymyxin, Polymyxin B/Maxitrol

Corticoids in Ophthalmic Pomade
- Dexamethasone 0.2% associated with oxytetracycline
- Dexamethasone 0.1% associated with neomycin and polymyxin B
- Triamcinolone 0.1% associated with neomycin—Cidermex

Injectable Corticoids
- Betamethasone: Celestone 4 mg/ml, Betnesol 4 mg/ml, Dexamethasone + triamcinolone-Soludecadron 4 mg/ml

Injectable retard corticoids

- Betamethasone-Celestone
- Triamcinolone
- Kenacord 40 mg
- Methylprednisolone-Depo Medrol 40 mg/ml

Evaluation of the Anti-inflammatory Action of Corticoids In Vivo
- Hydrocortisone-1
- Methylprednisolone 6
- Triamcinolone acetonide-48
- Betamethasone-35
- Dexamethasone-104

Systemic corticotherapy
- Treatment with systemically administered corticocosteroids is indicated in forms of serious chronic uveitis and relapsing uveitis, where administration prolonged use of steroids is complicated by their serious side effects.
- Systemic corticosteroids are the medication of choice in acute uveitis, but side effects can recommend other therapeutic options represented immunomodulators.
- The medication used in systemic corticotherapy is
  - Prednisone for oral administration
  - Methylprednisolone for intravenous use

Prolonged oral cortisone medication (3 months) requires continuous clinical surveillance and benefit/risk assessment especially in children. The duration of prolonged administration is depending on the course of uveitis, but gradual decrease of

cortisone treatment by 10% of the dose is necessary total at 8–10 days initially, then progressively depending on inflammation control

- after 4–6 months the dose may be 15 mg/day for the initial dose of 60 mg/day
- corticodependence is possible
- prolonged corticotherapy requires additional hydroelectrolytics, vitamins, calcium

Intravenous cortisone medication (bolus) will be adapted after patient age and existing Tare: HTA, diabetes, heart failure. The drug used is methylprednisolone-solumedrol with rapid diffusion, after IV administration (requires your supervision). High doses of corticoids are contraindicated in psychotic, treatment-induced hypopotesaemia (potentially fatal). Main extraocular complications in general treatment with corticoids: diabetes, epilepsy, HTA, heart failure, obesity, osteoporosis, psychosis, TB, gastrointestinal ulcer.

Stem cell treatment, multipotent stromal cells currently developing a favorable therapeutic perspective in the protocol of medication in uveitis.

- Stem cell therapy reduces inflammation in infectious uveitis through the ability their ability to manipulate the immune response and promote tissue regeneration, favorably influencing the course of bacterial, viral, fungal, parasitic infections
- Stem cell treatment should be applied concomitantly with systemic antimicrobial therapy.

Immunosuppressive medication

Immunosuppressants—medication for suppression of the immune system medication of choice for relapsing, chronic, disabling forms of uveitis.

- Alkylating agents-chlorambucil (leukeran), cyclophosphamide cyloxane, neosar)
- Antimetabolites
  - Folic acid analogues: methotrexate-first-line medication in AJ, indicated: LES, Wegener, Behcet, inflammatory enteropathies
  - Azathioprin-imuran, indicated in Behcet, Wegener, AJI
  - ofetil-cell CEPT mycophenolate
- Calcineurin inhibitors
  - Cyclosporine most commonly prescribed in the treatment of uveitis
  - Tacrolimus indicated in refractory uveitis, sympathetic ophthalmia, VKH
- Monoclonal antibodies—Rituximab-in the treatment of eye lymphoma, SLE
- Inhibitors of tumor necrotic factor alpha-anti-TNF alpha. Infliximab-remicad-indicated in…
  - Behcet, rheumatoid arthritis, Crohn's disease, ankylosing spondylitis
  - Adalimumab-humira
  - Etanercept-enbrel-indicated in: AJ, ankylosing spondylitis, rheumatoid polyarthritis
  - Ilk-2 receptor antagonists: daclizumab-zenapax

Immunomodulators

- Interferon—Avonex-Beta-1a-indicated in advanced S. M.
- Betaferon-Beta 1B-indicated in advanced S. M.
- Roferon-alpha 2A-indicated in: Behcet's disease, retinopathy in AIDS
- Introna-alpha 2b indicated in malignant melanoma

Indications of immunosuppressive medication in eye diseases

Immunosuppressive and immunomodulatory medication has indications in uveitis intermediate, posterior, chronic, relapsed, in uveitis in system diseases.

Ankylosing spondylitis—Severe forms of relapsing uveitis can benefit from treatment with: etanercept, infliximab, adalimumab

Juvenile rheumatoid arthritis—Prolonged corticotherapy with side effects can be replaced by

immunosuppressants-methotrexate with surveillance of side effects and etanercept.

Inflammatory enteropathies—Immunomodulators are effective in the long term and can decrease the dosage of corticosteroids azathioprine 2.5–3 mg/kg/day

Behcet's Disease—In patients with severe posterior uveitis who do not respond to corticotherapy, immunosuppressants are a reserve medication azathioprine, cyclosporine, cyclophosphamide, chlorambucil, etanercept, infliximab

LES—Immunosuppressive medication may be single or associated with oral steroids methotrexate, cyclophosphamide, rituximab

Nodular polyarteritis—cyclophosphamide, azathioprin, methotrexate

Wegener's Granulomatosis

- Improvement of prognosis was achieved by treatment with cyclophosphamide 2 mg/kg/day
- After reducing the dose of cyclophosphamide, continue treatment with methotrexate 20 mg/week

Intravitrean Immunosuppressants

- Methotrexate-in the treatment of lymphoma
- Sirolimus
  - immunosuppressant with antiproliferative properties that reduce inflammation intraocular in posterior uveitis
  - effective in endophthalmitis with negative cultures 440 ug
  - side effects-cataracts, glaucoma
- Infliximab
  - Used systematically in the treatment of autoimmune diseases
  - Side effects: reactivation of an infection(latent TB)
  - Indicated in uveitis from Behcet's disease, only when there are contraindications for IV administration.

Intravitreal injections with immunosuppressants are an alternative to medication systemic in Behcet, sarcoidosis, autoimmune diseases.

Surgical treatment in uveitis

It addresses complications and effectsoccurs only after careful control of uveal inflammation.

- Cataract
  - cataract surgery is done at least 3 months after remission of uveal inflammation with systemic corticotherapy.
  - Peroperative corticotherapy is required to reduce post-operative inflammation
  - The extraction of the lens with IOL and vitrectomy in pars plana is performed.
- Decompensated glaucoma if it requires surgical treatment can be done:
  - Trabeculectomy
  - Valva Ahmed

Anti-infectious treatment

- Treatment of bacterial infections-antibiotics
- Antiviral treatment
- Antiparasitic treatment

Treatment of bacterial eye infections—antibiotic therapy can be used (Table 11.10):

- curative: to treat infections
- prophylactic: in surgery

Empirical antibiotic treatment

If the identity of the germs is not known, treatment can be done initially empirical antibiotic: subsequent laboratory tests-culture-may or may not confirm identity germ

Targeted antibiotic treatment after germ recognition by culture

- Antibiotic therapy requires (Table 11.10):
  - germ recognition
  - localization of infection: superficial forms can be treated with local antibiotic; deep ocular, orbiting forms require antibiotics by the general route, Associated as needed with peri-, intraocular injections
- It is useless to associate antibiotics of the same class.
- Microbial flora in the healthy subject:
  - Saprophytic Flora:
  - Gram+: Staphylococcus epidermidis, micrococcus, corynebacterium, propionibacterium acnes
  - fungi: Candida, Trichophyton
  - Viruses
- Pathogens:
  - Gram+: Staphylococcus aureus, Streptococcus
  - Gram−: Acinetobacter, Enterobacteriaceae, Pseudomonas.

Table 11.10 Antibiotic sensitivity of pathogenic bacteria localized in the eye

	Sensitivity		
	++	+	Resistance
Staphylococcus aureus Negative Stavilococcus Cuagulozo	• Ceftazidime • Cefuroxime • Ciprofloxacin • Chloramfenicol • Vancomicin	• Fusidic Acid • Gentamicin • Amikacin	• Penicillin • Amoxicillin • Metronidazole
Streptococcus	• Ciprofloxacin • Fusidic acid	• Penicillin • Cefuroxim • Ampicilin • Cloramfenicol • Vancomicin	• Gentamicin • Amikacin • Metronidazol
P. acnes	• Vancomicin	• Penicillin • Ceftazidin • Cloramfenicol	• Ciprofloxacin • Gentamicin • Amikacin • Metronidazol
Bacillus sp.	• Cloramfenicol • Vancomicin • Gentamicin • Amikacin	• Cipfofloxacin	• Penicillin • Cefuroxim • Ceftazidim • Metronidazol
Neisseria g.	• Penicillin • Cloramfenicol • Fusidic acid	• Ciprofloxacin • Ceftazidim	• Vancomicin • Metronidazol
Hemophilia influenzae	• Penicillin • Cloramfenicol • Gentamicin • Amikacin	• Ceftazidim • Ciprofloxacin	• Vancomicin • Metronidazol
Pseudomonas	• Tazidim • Gentamicin • Amikacin	–	• Penicillin, ampicillin • Cloramfenicol • Vancomicin • Metronidazol
Anerobic	• Cloramfenicol • Metronidazol • Ceftazidim • Cefuroxim • Penicillin, ampicillin	• Vancomicin • Ceftazidim	• Ciprofloxacin • Gentamicin • Amikacin
Chloriformi	• Oxitetraciclin • Cloramfenicol	• Gentamicin • Amikacin • Ceftazidim	• Penicillin • Vancomicin • Metronidazol

- Germs in contact lens wearers:
  - Gram+: Staphylococcus aureus, Streptococcus;
  - Gram−: Pseudomonas, Klebsiella, Serratia, Enterobacter.
- Germs in conjunctivitis:
  - Gram+: Staphylococcus aureus 50%, Streptococcus 14%
  - Gram−: Enterobacter 3%, Moraxella + Acinetobacter, Hemophilus
  - Various

- Germs in keratitis:
  - Gram+: Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus acnes, Streptococcus, Corynebacteria
  - Gram-in contact lens wearers: Pseudomonas aeroginosa 20%, Enterobacter.
- Germs in acute endophthalmitis:
  - Gram cocci + 94%: Staphylococcus epidermidis 70%, Staphylococcus aureus 10%, Streptococcus 2%
  - Gram bacilli-6%.

Antibiotics

Betalactamine

- penicillins
- Methylcillin, Oxacillin, ampicillin, amoxicillin: indicated in infections Gram + bacilli, spirochetes, some species of Staphylococcus Golden, s. epidermididis
- Piperacillin, ticarcillin: Indicated in Gram (-) Pseudomonas germ, Enterobacter, Klebsiela
- cephalosporins
  - Are beta lactam ring antibiotics with antimicrobial activity
  - Generation I

    Cephalozoline (parenterally) used in the treatment of corneal ulcers combination with gentamicin, tobramycin, ciprofloxacin
    Cephalexin (p.o) effective against Gram (+) bacteria minimal effect on Gram (−)

  - Generation II: Cefuroxime, cefaclor with Generation I Spectrum plus Hemophilus, infections sinus
  - Generation III: Ceftazidine (fortum), ceftriaxone (rocefin) with resistant Gram (−) Spectrum to other Ab. Betalactam
  - Generation IV: Imipenem, meropenem active on enterobacter Hemophilus, Neiseria
  - betalactam inhibitors: clavulanic acid-indicated in streptococcal infections, Escherichia coli, Hemophilus
- Glycopeptides: Vancomycin-indicated in severe resistant infections given by Gram + type methicillin-resistant Staphylococcus in combination with cephalosporins III
- Antibiotics with selective effect of inhibition of protein synthesis
  - Broad spectrum

    Chloramphenicol-indicated in Haemophilus, Neisseria meningidis
    Tetracyclines: tetracycline, doxycycline. Minocillin with Gram (+) Spectrum and (−) rikes, chlamydia, Mycoplasma

– Moderate spectrum

Macrolides: erythromycin, azithromycin, clarithromycin with Spectrum: chlamydia, Mycoplasma coci Gram (+)
Ketolide-clindamycin in severe anaerobic infections, gram (+)cocci

- Narrow spectrum: Linezolid-active against Gram (+) resistant cocci
- Aminoglycosides are bactericidal inhibitors of protein synthesis assets per gram (−)
- Gentamicin, tobramycin, amikacin-active on anaerobic bacteria: E. coli, Enterobacter, Klebsiela, Proteus, Pseudomonas, Hemophilus, Moraxela
- Streptomycin-effective in TB
- Netilmicin-in the treatment of severe resistant infections
- Antimetabolites-sulfonamides, trimetropin active per Gram (+) (−) Chlamydia, Nocardia

Fluoroquinolones in Gram (−) Infections
- Generation I: norfloxacin
- Generation II: ciprofloxacin, ovofloxacin with gram (−) bacteria spectrum gonococcus, Gram (+) cocci, microbacteria, chlamydia
- Generation III: levofloxacin, moxifloxacin indicated in Gram (−) infections. gram (+) cocci, Enterococcus, methicillin-resistant Staphylococcus, anaerobes
- Antimicrobial solutions-commercial preparations: Ciprofloxacin, Gentamicin, Chloramphenicol, Neomycin, Ofloxacin, Sulfacetamide, Tobramycin

Fortified Topical Antimicrobial Solutions
- Amikacin = 25–50 mg/ml
- Bacitracin 10,000 u/ml
- Cefazolin, ceftazidime, cefuroxime 50 mg/ml
- Chloramphenicol 5 mg/ml
- Gentamicin 15 mg/ml
- Penicillin 5000 u/ml 0.3%
- Tobramycin 15 mg/ml
- Vancomycin-50 mg/ml

Drug associations between antibiotics or antibiotics and corticosteroids

- Antibioptal: Neomycin + Chloramphenicol
- Betabioptal: Chloramphenicol + Betamethasone
- Colbiocin
- Dexamethasone + Neomycin
- Garasone: Gentamicin + Betamethasone
- Maxitrol: Dexamethasone + Neomycin + Polymyxin B
- Ophtamesone: Neomycin + Betamethasone
- Spersadex: Chloramphenicol + Dexamethasone
- Tobradex: Tobramycin + Dexamethasone

Intraocular antibiotics:

- Aminosides:
  - Gentamicin 1 mg (Gram−)
  - Amikacin mg (Gram−)
- Cephalosporins Generation 3: −Ceftazidim (Gram+) 2.25 mg/0.1 ml BSS (do not mix with vancomycin-precipitate)
- Glycopeptides: −vancomycin-Gram + 1 mg in 0.1 ml or 0.05 ml of distilled water
- Vancomycin with amikacin 0.2 mg/0.1 ml BSS (macular toxic).
- Methicillin

Resistance of Bacteria to Antibiotics
- Natural resistance
- all suses of the same species are naturally resistant to an antibiotic
- for example, Enterobacteria are resistant to first-generation cephalosporins
- Resistance gained: resistance of golden Staphylococcus to: penicillin, methicillin, gentamicin, Vancomycin, Quinolone
- Resistant germ type can be present in healthy carrier, can create public health problems in hospitals and is responsible for nosocomial infections: Staphylococcus, Klebsiella, Enterobacter, Acinetobacter, Pseudomonas.
- It is necessary to change the antibiotic and antibiotic associations in order to antibiotics to be effective on resistant bacteria.
- In the treatment of infection antibiotics may be associated with corticotherapy which it acts on the inflammatory component of the disease.
- In the clinic it is initially necessary to perform a complete antibiotic therapy, adapted, before prescribing corticotherapy, it is also necessary to check the absence viral and/or fungal infection.
- Antibiotics are not prescribed for viral infection Antibiotics of the same class are not associated.
- Topical and systemic antibiotics basically they come from different classes.
- The dose of the antibiotic should be correct from the beginning but also in the high dose.

Antiviral medication in uveitis

Uveitis of Viral Etiology Is Rare:
- Ophthalmic shingles
- Dendritic epithelial keratitis with Uveal complication
- Retinitis with CMV

Topical Antivirals
- Iduviran
- Idoxyuridin-cholir 0.12%
- indicated in HSV recent epithelial form
- 1 drop per hour on the first day

- decreases the pace after the clinic and the course of the disease
- Zovirax-Acyclovir-pomade 3%
  - Indicated in herpetic keratitis
  - 1 drop 5/day continued 3 days after epithelialization
- Virophta-Trifluridin-colir
  - Indicated in HSV keratitis, keratouveitis
  - 1 drop/to 2 h drops up to 5/day 7 days
  - Continue treatment until healing
- Curative treatment of viral eye infection HSV, HZV [31] ZOVIRAX-Acyclovir-250, 500 mg vials at a dose of 10 mg/kgc at 8 h
- Prophylactic treatment of HSV eye infection ZOVIRAX-Acyclovir-tablets 200 mg/4 cp/day in 2 doses, re-evaluated at 6–12 months in eye surgery 4 cp/day in 2 intakes
- Curative treatment of CMV retinitis [40]
  - CYMEVAN, GANCICLOVIR-500 mg in CMV disseminated infections in AIDS-5 mg/kg in infusion every 12 h
  - FOSAVIR-FOSCARNET-attack 180 mg/kg/day, maintenance 90–120 mg/kg/day
  - CIDOFOVIR—treatment of CMV retinitis
  - 5 mg/kg-1 infusion/week

Antiparasitic Treatment
- Toxoplasmosis-pyrimethamine
- Amoebiasis-metronidazole
- Malaria-quinine-malocid
- Nematodes-albendazole
- Pinworms-piperazine-povanil
- Ankylostoma-levamisole
- Filaria-diethyl carbamazine-notezin-ivermetin-mectizan
- Bilhariasis-praziquantel
- Trypanosoma-pentamidine

Malaria Treatment

Antipaludic
- Natural-quinine
- For synthesis-chloroquine, hydroxychloroquine
- Pyrimethamine (malocide) used in the treatment of ocular toxoplasmosis 100 mg on the first day, then 50 mg/day until scarring on the FO
- Primaquin—Therapeutic alternative after chloroquine

Treatment in fungal eye infections

Fungal infections in the eyes are;

- Superficial-cutaneous, conjunctival, corneal, lacrimal pathways
- Deep-fungal endophthalmitis, orbital mucormycosis
- Canaliculitis-actinomices
- Cornea—Aspergillus, Candida, Fusarium
- Endophthalmitis-Candida, Aspergillus

Topical Ocular Antifungal

- Colir with imidazole
- Ketoconazole in boric acid 1–5%
- Fluconazole in BSS
- Itraconazole
- Ophthalmic pomade with fungizon, itraconazole
  - Subconjunctival injections-amphotericin B 0.15% (very painful)
  - Intravitreal injections-Fungizon 50 mg in 0.1–1 ml of water give the reaction brutal inflammatory

Antifungal-Systemic

- Polyene
- Fungistatics: Nystatin, trichomycin, pimaricin
- Fungicides: amphotericin b (fungizon), broad-spectrum macrolide antibiotics active on yeasts (Candida), filaments (Aspergillus), inactive on actinomices
- Pyridines
  - Fluorocytosine-ancothyl with action on yeasts
  - Imidazole-active on Candida albicans, sometimes on Aspergillus, Histoplasma, Cryptococus blastomices

Ketoconazole-Nizoral—Aspergillus, candida, fusarium
uconazole-triflucan—Aspergillus, candida, Cryptococcus
Itraconazole-sporanox—Aspergillus, candida, fusarium, histoplasma
Miconazole-dactarin-candida

Treatment of complications in uveitis

Iridocrystalinian synechia (posterior)—Mydriatic
Band keratopathy

- chelate formation with EDTA
- Excimer laser

Cataract

- surgery after reduction of inflammation (after 3 months minimum from extinguishing/relieving the inflammatory process)
- preoperative corticoids
- intraocular lenses

Glaucoma
- indication adapted by type of glaucoma
- topical
- carbonic anhydrase inhibitors
- antiglaucomatous surgery

Vitreous Opacities
- Short-cure corticoids
- Vitrectomy when needed

Vitreous Haemorrhage
- Clinical follow-up
- Vitrectomy when needed

N.V.R.
- Clinical follow-up
- FC laser if ischemia is present
- Interferon alpha

Cystoid macular edema-EMC

- It is a common complication in uveitis and is responsible for significant decrease in vision.
- Treatment in EMC comprises different stages with relative efficacy
  - Single or combination systemic NSAIDs
  - acetazolamide is ineffective in uveitic EMC
  - under local and systemic treatment with corticostherapy and/or immunosuppressants inflammation in uveitic Cem may decrease
  - in some EMCs the intravitreal dexamethasone implant may be effective in non-infectious uveitis
  - if EMC evolves, treatment with biological agents may be attempted

    MONOCLONAL antibody of antitumor factor—TNF using TOCILIZUMAB (TCZ) used to treat refractory rheumatoid arthritis
    TCZ-I. v. 8 mg/kg at 4 weeks infusion 1 h
    Monitoring: blood count, liver function tests, control OCT, identification of active inflammation

  - Use of antifouling agents
  - Vitrectomy in pars plana when needed
  - Periodic ocular Control of EMC 1, 3, 6 months after initiation treatment, with AV control, OCT, clinical identification of evolution treatment of uveitis and EMC by periodic indirect ophthalmoscopy.

DR
- treatment according to the type of DR: exudative, traction
- VPP
- reoperative coating with corticoids

Treatment of infectious uveitis is—Etiological causal treatment of posterior uveitis with antibiotics, steroidal anti-inflammatory drugs

Treatment of non-infectious uveitis

- Initial high-dose steroid treatment with progressive decrease in dosage to avoid inflammatory rebound
- In case of corticoresistance or corticodependence, or/and uveitis severe posterior to prevent relapses treatment will be instituted immunosuppressant
- in Behcet at the first episode of panuveitis azathioprin is indicated—in case of ocular inflammation refractory to immunosuppressants are indicated anti-TNF-alpha, in particular monoclonal antibodies—ADALIMUMAB and INFLIXIMAB in Behcet (severe) AJI
- interferon-alpha immunomodulators are effective in Behcet for vasculitis and neovascularization

Treatment of uveitic macular edema

Uveitic macular edema is present in 30% of uveitis and is serious, because it is accompanied by the important decrease in AV.

The most common etiology of macular edema in uveitis is:

- chorioretinitis Birdshot—100%
- idiopathic intermediate uveitis-60%
- chronic uveitis associated with AJI, uveitis from sarcoidosis, Behcet
- toxoplasmic chorioretinitis
- heterochromia Fuchs
- anterior uveitis with HLA-B27

Treatment of uveitic EM must be instituted early and causally in order to be effective, since the decrease in AV can be irreversible. Treatment is complex.

- local
  - topical, periocular, subtenonian dexamethasone
  - intravitrean-antifouling, triamcinolone ozurdex
- systemic
  - oral steroidal anti-inflammatory i. v.
  - antitnf, interferon, abetacept, tocilizumab, sarilumab
  - TIO control
- surgical
  - if necessary, according to the etiology of EM
  - cataract
  - glaucoma

Treatment in retinal vasculitis

Retinal vasculitis can complicate the course of an intermediate uveitis, or hindquarters

- in intermediate uveitis—vasculitis is peripheral and predominantly venous
- in posterior uveitis-vasculitis is venous, arterial, mixed

Retinal arterial vasculitis:

- infections: HSV, Lyme, syphilis, TB
- system diseases: Behcet, LES, Wegener, Susac
- ectastic arteritis-idiopathic retinal vasculitis, macroaneurismus arteriolar, neuroretinitis

Retinal venous vasculitis

- systemic diseases: sarcoidosis, Behcet, Ms, SLE, scleroderma, polyarthritis rheumatoid, nodular periarteritis, Crohn's
- eye diseases (probably immune)—Birdshot, intermediate uveitis, ophthalmia nice, Irvine-Gass
- infections: viral (HSV), bacterial (syphilis, TB, endophthalmitis), parasitic (toxoplasmosis, toxocarosis, oncocercosis), mycotic
- tumors: non-Hodgkin's primitive intraocular lymphoma, acute leukemia

Retinal vasculitis associated with Irian nodules:

- sarcoidosis
- sympathetic ophthalmia
- TB, syphilis, leprosy

Retinal vasculitis associated with retrocorneal precipitates

- large precipitates:
  - systemic diseases: sarcoidosis
  - infections-toxoplasmosis, syphilis, HSV
  - sympathetic ophthalmia
  - lymphoma
- fine precipitates: systemic diseases: Behcet, sarcoidosis, collagenoses
- Birdshot: metastases, lymphoma, retinoblastoma

Hypopion uveitis associated with vasculitis

- ankylosing spondylarthropathies in prolonged, insufficiently treated inflammations
- uveitis with hypopion can mask posterior uveitis in Behcet, endophthalmitis, tumors

Vasculitis associated with multiple foci:

- retinas
  - infections: toxoplasmosis, toxocarosis, HSV, candida, syphilis, TB, onchocercosis
  - systemic diseases-Behcet

- choroid
  - pseudohistoplasmosis
  - Birdshot
  - sarcoidosis
  - sympathetic ophthalmia
  - TB

Occlusive retinal vasculitis in:

- Behcet
- sarcoidosis
- infections: toxoplasma, HSV, syphilis, TB

Retinal vasculitis by age

- under 5 years
  - infections: toxocarosis, viral retinitis
  - inflammation: AJI, juvenile xanthogranuloma
  - neoplasms: retinoblastoma, leukemia
- 5–15 years
  - toxocara, toxoplasma
  - sarcoidosis
  - leukemia
- 20–60 years
  - toxoplasma, syphilis
  - sarcoidosis, Behcet
- >60 years—lymphoma, metastases

Treatment

- From the very beginning, depending on the establishment of the causative factor of vasculitis should eliminate infectious tumor causes.
- immunosuppressive treatment can aggravate the infectious process
- may be started cortisone treatment, or antibiotic treatment in function of suspicions

Symptomatic Treatment

- systemic corticotherapy × methylprednisolone bolus 3 days, followed by prednisone 1 mg/kg/day 3 weeks, after which the dose is progressively reduced
- corticotherapy in combination with immunosuppressants
- thiopurines
  - Azathioprin (imuran)—in Behcet
  - Mycophenolate mofetil (cellcept) in refractory uveitis

- calcineurin inhibitors
  - Ciclosporin (neoral)—in Birdshot
  - Dihydroreductase (methotrexate)—in uveitis in children
- alkylating agents
- Cyclophosphamide (endoxane)
- Chlorambucil (chloraminophen) (in Behcet)
- Tacrolimus—in refractory uveitis

Side effects of immunosuppressants are: infectious, hematological, oncogenic, nephrotoxic

- if these effects are important, it is recommended to use immunomodulator
- Corticotherapy in combination with immunomodulators
- monoclonal antibodies or polyvalent immunoglobulins tegelin—indicated in Birdshot
- monoclonal antibodies are anti-TNF-a-infliximab-indicated in relapsing uveitis in Behcet effective within the first 24 h
- interferons INF have antiviral, antiproliferative and immunomodulators—indicated in Behcet, most commonly using ROFERON-INF-a-2A and sometimes VIRAFERON-INF-a-2B

Treatment of hypertensive uveitis

In the face of hypertensive uveitis should be eliminated cortisone HTIO after: clinical features and paraclinical balance with Gonioscopy

- anti-inflammatory treatment may reduce HTIO
- if necessary, General htio treatment with diuretics and local is done

Causes of hypertensive uveitis

Anterior uveitis

- HSV, HZV, CMV
- Sarcoidosis
- TB
- Fuchs heterochromic cyclitis
- AJI
- Syphilis
- Posner Schlossman

Intermediate Uveitis

- Lyme disease—toxocaroza
- TBC-SM
- Arcoidoz-limfom oculo-cerebral
- Sifilis

Uveit Euro posterioar Euro

- toxoplasmosis-ophtalmic sympathetic
- sarcoidosis-VKH
- TB–RNA
- Syphilis–Behcet

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Chapter 12
Ophtalmological Pathology and Management in Eye Diseases: Retina Distrophies and Degenerations

Marieta Dumitrache

Abstract **Retinal distrophy at the nivel of the rods**, retinitis- retinitis pigmentoza- is a hereditary group of diffuse idiopathic familiar, progressive retinal dystrophies wich be accompanied by posterior subcapsular cataract, open angle glaucoma, myopia, keratoconus, intermediate uveitis. RP is presents in syndromes. **Retinal dystrophies at the level of the cones** are: Startgardt disease, fundus flavimaculatus, progressive con/dystrophies, Bests' disease. **Choroidal dystrophies** are choroideremie, gyrate athrophie. **Vitroretinal dystrophies** are: retinoschizis congenital, Goldman Favre. **Vitreoretinal degenerations** are: Wagner Jansen, Stickler syndrome. **Peripheric retinal degenerations** may be lattice degeneration, degenerative retinoschizis.

Keywords Retinal dystrophies · Retinitis pigmentozas · Stargardt disease · Fundus flavimmaculatus · Best's disease · Choroideremie · Gyrate athrophie · Retinoschizis · Lattice degeneration

Retinal, Choroidal and Vitreal Dystrophys and Degenerations

- Retinal dystrophies
  - at the level of the rods—Retinitis pigmentosa
  - at the level of the cones—Stargardt's disease, Best's disease, familial drusen
- Choroidal dystrophies—choroideremia, gyrate atrophy

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- Vitreoretinopathy: congenital retinoschisis, Goldman Favre disease, Wagner, Jansen, Stickler syndrome
- Peripheral retinal degenerations: degenerative retinoschisis, lattice degeneration

Vascular Diseases of the Retina

- Amaurosis fugax
- Retinal artery occlusion
- Retinal vein occlusion
- Hypertensive retinopathy
- Toxemia of pregnancy
- Diabetic retinopathy
- Retinopathy of prematurity
- Wyburn-Mason disease
- Coats disease
- Leber miliary aneurysm
- Retinal telangiectasia
- Eales disease
- Retinopathy in blood diseases

METABOLIC DISEASES OF THE RETINA: sfingolipidoses, mucolipidoses, mucopolysaccharidoses.

Phacomatoses—Neurocutaneous Syndromes

- Retinal angiomatosis—von Hippel Lindau
- Neurofibromatosis type I—von Recklinghausen
- Neurofibromatosis type II
- Bourneville tuberous sclerosis
- Encephalofacial angiomatosis Sturge-Weber-Krabbe syndrome
- Louis-Bar syndrome
- Racemic hemangioma - Wyburn-Mason disease

Vasculitis

- Horton temporal arteritis
- Takayasu arteritis
- Polyarteritis nodosa (Periarteritis)—PAN
- Kawasaki disease
- Granulomatosis with polyangiitis

- Wegener's granulomatosis
- Churg-Strauss eosinophilic granulomatosis

Infectious-Inflammatory Diseases of the Retina

- Bacterial retinochoroiditis, viral retinochoroiditis, parasitic and fungal retinal infections**SYSTEMIC AND OCULAR INFLAMMATORY PATHOLOGY.**

  WHITE DOTS CHOROIDAL SYNDROMES.
  non-AMD MACULAR PATHOLOGY.

Retinal, Choroidal and Vitreal Dystrophy and Degeneration

Retinal dystrophies

- **at the level of the rods**
  - retinitis pigmentosa
- **at the level of the cones**
  - ***Dystrophies of the neuroepithelium***

    Stargardt disease, Fundus flavimaculatus
    Progressive cone dystrophy
    Albinism
  - ***RPE dystrophies***

    Best disease
    Network dystrophy of EP
  - ***Dystrophies of RPE and Bruch's membrane***

    Familial drusen
  - ***Dystrophies of RPE and choroid***

    Central areolar choroidal atrophy
    Sorsby pseudoinflammatory dystrophy

Choroidal Dystrophies

- gyrate atrophy
- choroideremia
- diffuse chorioretinal atrophy

Vitreoretinopathy

- Vitreoretinal dystrophies

  Congenital retinoschisis.
  Goldmann Favre disease

- Vitreo-retinal degenerations

  Wagner syndrome, Jansen syndrome, Stickler syndrome
  Familial exudative vitreoretinopathy

Peripheral Retinal Degenerations

- benign

  degenerative retinoschisis

- predisposing to RD

  snail track degeneration
  lattice degeneration

Retinal Dystrophies

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Retinal Dystrophy at the Level of the RODS

Retinitis Pigmentosa (RP)

- Retinitis pigmentosa is a hereditary group of diffuse, idiopathic, familial, progressive retinal dystrophies affecting the rods.

- RP manifests itself at 30–40 years of age, with nyctalopia, is bilateral, more frequent in men (3/2) and progresses to blindness.
- RP has a great genetic diversity AD, AR, XLR, sporadic, AD forms have the best prognosis, XLR forms have the most severe prognosis [1].
- RP can be accompanied by: posterior subcapsular cataract, open-angle glaucoma, myopia, keratoconus, vitreous changes, intermediate uveitis, ON drusen.
- Visual symptoms
  - Hemeralopia (nyctalopia—hesperanopia) is the decrease in VA at night (it is the first symptom perceived by the patient) associated with photophobia and field loss.
  - AV decreases by genetic form: early in XLR, late in AD, with preservation of central AV.
  - The visual field changes slowly, starting from the middle periphery of the retina with annular scotoma that widens towards the center and periphery; Initial altered CV is progressively lost to tubular CV.
  - Colour vision–yellow/blue dyschromatopsia.
- Functional investigations—ERG–prolonged dark adaptation, eventually ERG becomes extinguished.
- Fundus [2]
  - initially the fundus is normal, but with variable ERG alterations;
  - the first manifestations in RP concern the arteriolar caliber which is thin and is associated with subtle pigmentary changes;
  - in time the triad appears;

    RP with intraretinal pigmentary changes in the form of perivascular bone corpuscles (osteoblasts) located in rods in the equatorial region with subsequent extension from the periphery of the retina to the center;
    small caliber arterial vessels;
    waxy disc pallor with optic atrophy;

  - other possible associations: choroidal sclerosis, exudates, papillary drusen, cystoid macular edema, cellophane maculopathy, atrophic maculopathy.
- **Atypical RP**
  - Sector RP is frequently located in the nasal quadrant
  - RP sine pigmento with clinical manifestation of RP but without the osteoblastic pigment
  - Retinitis punctata albescens associated with numerous scattered white/yellowish spots
  - Paracentral RP in which pigmentation involves the papilla and vascular arches
  - RP and exudative vasculopathy that looks like Coats syndrome

Treatment

- periodic ophthalmological clinical follow-up for the detection and treatment of associated eye conditions.

- there is no curative treatment in RP
- nutritional supplements, antioxidants, vitamins (Vitamin A administered orally, 15,000 IU/day, delays the appearance of ERG changes but does not significantly influence the evolution of visual acuity and visual field)

  High doses of vitamin A, administered for a long time, have teratogenic effects, are hepatotoxic and cause osteoporosis
  Vitamin E would not be indicated in the treatment of RP because it could accelerate the progression of the disease
  Acetazolamide, given systemically for cystoid macular edema—is controversial
  Lutein provides protection against oxidative damage
  Antioxidants
  Docosahexaenoic acid

- Gene therapy–intravitreal, subretinal
- Correction of refractive errors with dark lenses
- Cataract surgery after clinical assessment.
- **RP may be associated with systemic abnormalities** [3–5]
  - ***Bassen syndrome–Kornzweig –abetalipoproteinemia***
  - AR

    Atypical RP—no osteoblastic spicules
    secondary to vitamin A deficiency

- possible death from heart rhythm disturbances

Ophthalmology
- RP
- ptosis
- squint
- ophthalmoplegia
- nystagmus

Sistema
- steatorrhea
- abdominal distension
- spinocerebellar ataxia
- areflexia
- peripheral neuropathy
- acanthocytosis
  - Management: Fat-restricted diet
  - Treatment:

    Vitamin A = 100–400 IU/kg/day
    Vitamin E = 2400–12,000 IU/kg/day
    Vitamin K = 5 mg orally

Omega 3 fatty acids = 0.10 g/kg/day
Folic acid

- ***Alstrom syndrome***
  - AR
  - Early photophobia and nystagmus with profound decrease in VA (visual acuity) to CF (count fingers) by age 20
  - Ocular: **RP**, cataract
  - Systemic:

    obesity
    insulin-resistant diabetes
    diabetes insipidus
    liver cirrhosis
    kidney damage with chronic progressive nephropathy
    hypogonadism

  - Adequate treatment for conditions
  - ***Cockayne syndrome I, II***
  - AR
  - Ocular

    RP
    enophtalmos
    squint
    farsightedness (+10 D)

  - Systemic:

    growth disorder and intellectual deficit with progeroid facies, small head, disproportionately long legs, skeletal malformations
    progressive sensorineural deafness
    ataxia, epilepsy, extrapyramidal signs
    intracranial calcifications
    cerebral atrophy

- ***Kearne-Sayre syndrome***
  - it is a mitochondrial cytopathy
  - Ocular:

    Diffuse RP, more pronounced in the macula
    Progressive external ophthalmoplegia
    Bilateral ptosis

  - Systemic:

    cardiac conduction defect
    ataxia
    growth disorder

mental impairment
deafness

- Management—coenzyme Q has a discrete effect on eye movements, atrioventricular block
- ***Refsum disease***
- metabolic disease with onset around 10 years
- AR
- the absence of the enzyme that oxidizes phytanic acid
- children,ocular manifestations:

  Progressive RP:
  nystagmus
  pale optic disc
  thin arteries
  macular atrophy
  cataract

- Systemic:

  facial dysmorphism
  mental retardation
  hepatomegaly
  severe progressive deafness

- adults, ocular manifestations:

  RP
  Pigmentary and atrophic changes at the macula
  Cataract
  Pupillary abnormalities
  Optic atrophy

- adults, systemic manifestations:

  cerebellar ataxia
  anosmia
  deafness
  ichthyosis
  cytoalbuminuric inversion in CSF

- Management:

  Restrictive phytanic acid diet - animal fat (fish, lamb, veal), milk and green vegetables
  In Refsum disease, only 10–20 mg phytanic acid/day is needed
  The faster the diet is initiated, the smaller the lesions and the better prognosis
  Plasmapheresis—helps when the general condition is deeply affected, it is indicated in:

Ineffective diet
Patients non-compliant with the diet
The serum concentration of phytanic acid is greater than 900 μmol/L

- ***Zellweger syndrome***–adrenoleukodystrophy (infantile form of Refsum disease) with: severe RP with pigment dispersion without osteoblasts, congenital amaurosis, pulmonary disease, skeletal, renal manifestations, seizures, possible death in the first year.
- ***Cogan syndrome***—RP, deafness
- ***Stickler syndrome***—RP, deafness
- ***Usher syndrome***
- Ocular:

  RP with decreased VA and variable nyctalopia, depending on the type of syndrome I → IV

- Systemic:

  Deafness ± vestibular impairment
  Mental retardation

- Management:

  Avoid ototoxic drugs - aminoglycosides
  Cochlear implant if needed

- ***Bardet-Biedl, Lawrence-Moon syndrome***
- AR
- Ocular:

  RP (80%) with macular involvement
  Profoundly decreased AV towards 30 s (possibly blind)
  Eye fundus with salt and pepper appearance or bony spicules
  Nystagmus
  Posterior cortical cataract
  Myopia
  Pigmentary vitreous syneresis
  Short palpebral fissure
  Macular edema
  Secondary optic atrophy

- Systemic:

  Small stature
  Mental retardation
  Congenital obesity 95%
  Hypogonadism
  anosmia
  Partial deafness

- Syndromes:

  Bardet-Biedl—presents with polydactyly and syndactyly
  Lawrence-Moon—spastic paraplegia, without polydactyly

- **Pseudo-Retinis pigmentosa** can be present in:
- infectious inflammatory eye diseases: toxoplasmosis, rubella, syphilis
- post CRVO—diabetic retinopathy
- post-traumatic
- post-medication: chloroquine, chlorpromazine
- Conditions that can produce hemeralopia: gyrate atrophy, choroideremia, vitamin A deficiency

Retinal Dystrophies at the Level of the Cones

Dystrophies of the Neuroepithelium

Stargardt disease *Fundus Flavimaculatus*

Stargardt disease

- Both diseases present clinically different manifestations of the same disease, with onset in the first decade of life, with bilateral symmetrical evolution
- It is a rapidly progressive hereditary juvenile macular dystrophy, associated with flavimaculate spots with polymorphic manifestations [6, 7]
- AR, 1p21–22, ABCAR gene
- Onset at 10–20 years with progressive deterioration of central VA and visual field with central scotoma.
- symptoms
  - decreased central vision, bilaterally
  - in juvenile and flavimaculate forms, the VA decrease is rapid and severe
  - retain a 1/20 VA
  - color vision—red/green dyschromatopsia 50%, yellow/blue 8%
- ERG—photopic—normal, diminished, scotopic—normal
- EOG—abnormal in evolutionary forms
- FA—"choroidal quiescence" by lipofuscin deposits from RPE and "window" effect by macular lesions
- Fundus
  - macular

    disappearance of the foveolar reflex
    atrophic maculopathy with oval areas, with a "snail slime" appearance surrounded by white/yellow flavimaculate spots

geographic atrophy with bull's-eye appearance (FA foveal disinterest) 'beaten metal', 'inverted egg'/marked hyperfluorescence in foveola terminal—chorioretinal atrophies and RPE with highlighting of the great vessels or only central areolar choroidal atrophy

  - extramacular

    white/yellow flavimaculate lesions under the retinal vessels, isolated or confluent

- Prognosis—reserved with progressive decrease in VA, and stabilization around 1/10 by 30 years.***Fundus flavimaculatus***
- AR
- **Late onset in adults, with symmetrical bilateral lesions with progressive loss of central vision** [8]
- ERG
  - photopic—normal, low
  - scotopic—normal
- EOG—abnormal
- Color vision - normal
- Fundus
  - white/yellowish, poorly defined flavimacular spots in posterior pole and mid-periphery
  - specific color (darker—vermillon) at the fundus in 50%
  - geographic (sometimes) macular atrophy

Progressive Cone Dystrophy

- Genetically heterogeneous with sporadic forms, AD, AR, XLR
- Onset at 10–30 years, with progressive loss of central vision and color vision and frequent disabling photophobia preceding the macular lesions [9]
- color vision - deutan/tritan deficit
- ERG
  - decreased photopic response
  - confirms the diagnosis and specifies the association of cone and rod involvement
- FA
  - round hyperfluorescence with "window" effect, with hypofluorescent center
- FFundus

  - macular pigmentary rearrangement, pigment deposits along the venous branches
  - "bull's eye" appearance that may or may not progress to macular atrophy with respect to the foveola
- prognosis
  - decrease in VA towards 40 years

Other Causes of "Bull's Eye" Maculopathy

- Chloroquine maculopathy
- Benign concentric annular macular dystrophy
- Batten disease

Albinism (Table 12.1)

- Hypopigmentation of both eyes and/or skin due to tyrosinase deficiency, which converts tyrosine into melanin.
- Albinism has the form: (Table 12.1)
  - Oculo-cutaneous

    Tyrosinase-negative
    Tyrosinase-positive
  - ocular

Dystrophies of the Pigment Epithelium

- **BEST disease—**vitelliform macular dystrophy
- Hereditary maculopathy with early lesions and abnormal EOG, the most common childhood macular dystrophy with progressive evolution and slow deterioration of bilateral vision [11, 12]
- AD, chromosome 1 1q13, bilateral, asymmetric, in both sexes

Clinical

- Initially asymptomatic 75%
- Macular lesions with stadial evolution
  - Stage 0—normal fundus, EOG abnormal
  - Stage 1—previteliform

Table 12.1 Clinical forms of albinism [10]

Oculo-cutaneous albinism		Ocular albinism
Tyrosinase-negative	Tyrosinase-positive	Ocular
– AR – inability to synthesize melanin – skin: blond hair, discolored skin – ocular: – hypoplastic iris; absence of pigmentation; – Fundus—has an orange color, with the visibility of large vessels and foveolar hypoplasia – refractive anomalies – red reflex in the pupil due to the lack of iris pigment – Photophobia – VA < 1/10 – pendulum and horizontal nystagmus, increases with illumination – the chiasma has a reduced number of direct fibers	– AR/genetic complexity – partial melanin synthesis capacity – variable hypopigmentation of the fundus – Low VA in relation to foveolar hypoplasia – associated syndromes: CHEDIAC HIGASHI—recurrent infections due to leukocyte abnormalities HERMANSKI PUDLAK with platelet dysfunction	– XLR – in pregnant women – iris, retinal depigmentation without skin depigmentation – foveolar hypoplasia or aplasia – VA reduction nystagmus

discrete macular pigmentary changes with "egg yolk" appearance or "sunset"
EPR window defect on FA;

- Stage 2—viteliform at 10–20 years with a spread (scrambled) "egg yolk" appearance consisting of lipofuscin
- Stage 3—pseudohypopion due to partial resorption of lipofuscin with yellowish hyaline material with fluid level—low VA
- Stage 4—disaggregation of the vitelline lesion with large decrease in VA: 4a atrophy, 4b macular scar, 4c choroidal neovascularization

- ERG—normal
- EOG—abnormal even in persons with normal fundus with increasing Arden index
- Prognosis—VA is good until 50 years old, then declines through macular scarring, NVC, geographic atrophy, macular hole.
- Treatment
  - Genetic counseling
  - Professional orientation

Network Dystrophy of RPE

- Extremely rare, childhood-onset AD

- *macular degeneration in "butterfly wings"*

  AD, discovered incidentally, at 20–50 years, has moderate decrease in VA. Yellowish pigmentation at the macula "butterfly wings" with normal VA, visual field, pathological EOG

- *SJÖGREN retinal dystrophy*—pigmentary tracts on fundus with normal macula
- *macroreticular dystrophy*—pigmented tracts on the foveola with radial disposition

Dystrophies of RPE and Bruch's Membrane

Familial Dominant Drusen [13]
- AD, 2q16 with onset at 20–30 years, but also at 60 years, bilateral, symmetric
- May be asymptomatic until macular degenerative lesions set in or variable VA decrease, difficulty reading, distorted images
- Fundus—drusen—are small prominent round yellow-white spots (around 30 years old), which increase in number and surface over time
  - Large serous macular and peripapillary drusen (around 50 years)
  - RPE changes, geographic macular atrophy
  - CNV, OMC
  - *in* Leventine's disease - small drusen of the basal lamina with a radial disposition centered on the fovea and parapapillary with a decrease in VA towards the age of 60 due to geographic atrophy and CNV.

Dystrophies of RPE and Choroid

Central Areolar Choroidal Atrophy
- Primary involvement of the RPE and choriocapillaries, with disappearance of the RPE, photoreceptor choriocapillaries, and sclerosis of the choroidal great vessels, but with normal inner retinal layers.
- Primitive—isolated macular lesion AR, AD with macular atrophy and extensive atrophic lesions in the posterior pole with normal choroidal vessels or white cords.
- Secondary—macular lesions in: Stargardt disease, fundus flavimaculatus, cone dystrophy, RP, viteliform disc.

Sorsby Pseudo-Inflammatory Dystrophy
- AD, onset at 50 years old, with bilateral VA decline
- Fundus—asymptomatic, confluent, drusen-mimicking deposits along the vascular arches, nasal to the papilla, and in the midperiphery
  - exudative maculopathy responsible for decreased VA
- Reserved prognosis

Other Retinal Dystrophies

- **Vitelliform foveolar dystrophy of the adult** [14]
  - AD, onset 40–60 years old with metamorphopsia, fundus with small round yellowish foveolar lesions
- **Multifocal vitelliform disease**
  - adults, no family history, normal EOG
- **Dominant cystoid macular edema**
  - AD, onset 10–20 years old, progressive loss of central vision
  - Bilateral OMC unresponsive to acetazolamide
  - FA foveolar diffusion in "flower petal"
  - Reserved prognosis
- **Biety crystalline dystrophy**
  - AR, onset 30 years old, with progressive decrease in VA with white-yellow crystals in the posterior pole and crystalline keratopathy.
- **Alport syndrome**
  - XLR
  - Fundus with yellowish spots or flakes, dispersed perimacularly or peripherally
  - Associated with: anterior lenticon, posterior corneal dystrophy, deafness, chronic renal failure
  - Good prognosis
- **Benign familial flavimaculate retinal spots**
  - AR
  - Fundus: yellowish-white spots, surrounding the macula
  - asymptomatic
- **Leber congenital amaurosis**
  - AR, 17p gene, is the most severe form of retinal degeneration produced by various genetic mutations
  - **It is responsible for 10% of cases of blindness**
  - It was considered the infantile form of RP with significant vision loss, up to blindness, in the child
  - May begin as congenital blindness with oculodigital sign present in the newborn and diminished or absent pupillary reflexes
  - Symptoms: decrease in visual acuity from 1/10 to LP or no LP
  - Fundus has a variable appearance, from normal to various modifications:

    Decrease in arteriolar caliber
    Chorioretinal atrophy
    Macular coloboma-like lesions

Retinitis pigmentosa ranging from the appearance of bony spicules to "salt and pepper" pigmented lesions
Optic atrophy

– Eye associations:

Important refractive errors - hypermetropia
Keratoconus, keratoglobus
Nystagmus, strabismus
Cataract

– Systemic associations:

Mental handicap
Deafness
Epilepsy, CNS abnormalities
Renal abnormalities
Skeletal malformations
Endocrine dysfunction

– Reserved prognosis

- **Congenital stationary nyctalopia (CSN) with normal Fundus**
  - CSN Nogaret—AD, mild ERG impairment for cones, normal for rods
  - CSN Riggs—AD, ERG is normal for cones
  - CAN with myopia—has an AR form and an XLR form (Schubert-Bornschein type)
- **Stationary congenital nyctalopia with abnormal Fundus—Oguchi disease**
  - AR, 13q34, 2q37
  - Fundus presents:

The dark adaptation time of the cones is extended to several hours
Fundus color changes—Mizuo phenomenon

Fundus after light adaptation is yellowish-brown
Fundus after dark adaptation for 12 h is normal

- ***Fundus albi punctatus***
  - AR, chromosome 12q 13, 14
  - FO shows small yellowish-white spots in the posterior pole with peripheral extension, with sparing of the macula
  - ERG normalizes in scotopic recordings after 4–8 h of dark adaptation
  - Alport *syndrome*

Ocular
- Anterior lenticonus
- Polar cataract
- Fundus with punctatus appearance

Systemic
- Deafness
- Renal insufficiency

Choroidal Dystrophys

- They are conditions accompanied by atrophy of the RPE and of the choriocapillaries that allow the visibility of the large vessels [9, 15].

Choroideremia

- Choroideremia is a degenrative XLR disorder characterized by progressive degeneration of the RPE and choroid, produced by diffuse, progressive, bilateral atrophy of the choriocapillaries and RPE, with visibility of the choroidal vessels [5, 16]
- Beginning:
  - night blindness
  - photophobia
  - constriction of the visual field
  - central vision is maintained
- Symptoms:
  - around the age of 10 the difficult adaptation to darkness and hemeralopia begins
  - vision loss begins around age 30
  - in the progression of the disease, visual field restrictions appear with peripheral constriction and significantly reduced vision towards 40–50 years
- Early fundus changes occur in the middle periphery:
  - focal atrophy of RPE
  - regional choroidal atrophy with exposure of large vessels
  - diffuse choroidal thinning and choroidal vascular thinning
  - choroidal atrophic areas, diffuse peripheral, circumscribed become coalescent
  - there are also areas of normal choroid in the macula and peripheral retina
  - the optic disc is pale
- Associated signs:
  - fibrillary degeneration of the vitreous
  - posterior subcapsular opacities
  - myopia

- Prognosis—most patients have useful vision until the age of 60, with visual acuity declining profoundly after this age

Gyrate Atrophy

- Progressive, bilateral, AR condition related to deficiency of ornithine aminotransferase (OAT), the mitochondrial enzyme that converts ornithine [17, 18].
- It is accompanied by hypolysinemia and hyperornithinuria
- Genetic disease, produced by mutation of chromosome 10.
- Gyrate atrophy is a progressive choroidal dystrophy characterized by well-defined areas of atrophy of the RPE and choroid
  - initially the middle periphery of the retina is affected, with subsequent extension in the periphery and central, late the damage being diffuse
- The onset is up to 20 years with nyctalopia
- symptoms
  - progressive hemeralopia with onset at 10–20 years, complete blindness at 70 years
  - the visual field shows scotomas in the middle periphery, which unite to form an annular scotoma with extension towards the periphery and center
  - accompanied by:

    medium myopia, astigmatism
    posterior subcapsular cataract towards the age of 30
    chorioretinal and macular atrophy at age 40
- Fundus presents areas of chorioretinal atrophy, yellowish, round, with scalloped edges with progressive extension, initially located in the mid-periphery, with late macular involvement
- Complications:
  - cataract
  - OMC
  - macular pucker
- Treatment:
  - correction of refractive error: myopia, astigmatism
  - **arginine-deficient diet**, by restricting arginine-rich foods (nuts, vegetables), low-protein diet
  - genetic counseling

Diffuse Choroidal Atrophy

- AD
- Onset at 40–50 years with decreased central visual acuity and nyctalopia.
- Fundus shows quasi-total choroidal atrophy, progressive, with peripheral extension.
- Poor prognosis if macular involvement is early.

Helicoid Peripapillary Chorioretinal Degeneration

- AD
- Onset in a child with chorioretinal atrophic bands with slow extension from the papilla.
- There is a severe form in young people and a moderate form in the elderly.

Pigmentary Paravenous Retinochoroidal Atrophy

- Osteoblastic pigmentation along the large retinal veins with adjacent chorioretinal atrophy.
- Progressive bifocal chorioretinal atrophy—extensive atrophic chorioretinal foci located temporally and nasally, separated from a normal area
- Reserved prognosis by macular touch.

Vitreoretinal Degenerations

Vitreoretinal Dystrophies

Congenital Retinoschisis

- Abnormality of the Müller cell layer, with cleavage of the retinal nerve fiber layer (in senile retinoschisis, the cleavage is outside the plexiform layer) [19, 20].
- Retinoschisis is present in males at birth, with rapid progression towards 5 years and stabilization at 20 years old.
- Foveal retinoschisis (with 50% abnormalities):
  - cystoid lodges with radiating striae arranged widely, centered on the fovea
  - cystoid structures are round microcysts in the perifoveal area accompanied by marked pigmentary degeneration

  - ruptured cavitary schisis bubbles, accompanied by possible vitreous hemorrhages
  - sclerosis and vascular blockages
  - vitreous flakes
- Peripheral retinoschisis:
  - oval holes located in the inner leaf
  - located infero-temporally
  - hypermetropia
  - reduction of visual acuity, but it can also be normal visual acuity
- Visual field—absolute scotoma in peripheral retinoschisis.
- Complications:
  - vitreous hemorrhages
  - retinal detachment
- ERG—in the peripheral retinoschisis appears the selective diminution of the *b wave*, compared with the amplitude of the a wave *in* scotopic and photopic.
- EOG—abnormal in peripheral retinoschisis

Goldmann-Favre Disease

- It is a rare vitreoretinal degeneration, AR, with nyctalopia and constriction of the visual field (RP + juvenile retinoschisis) [5].
- Onset in childhood, with nyctalopia, decreased vision
- Clinical signs:
  - vitreous degeneration with mobile veils
  - central and peripheral retinoschisis
  - attenuated vascular caliber
  - peripheral osteoblastic pigment
  - lattice degeneration
  - arborescent white peripheral retinal vessels in dendritic form
  - pale optic disc
  - cataract
- ERG—reduced.
- EOG—abnormal in forms with juvenile retinoschisis.
- Reserved prognosis.
- Management:
  - permanent clinical follow-up
  - surgical treatment of retinal detachment.

Vitreoretinal Degenerations

Wagner Syndrome

- AD, chromosome 5q13, 14, 12q13
- Ocular:
  - medium myopia
  - cataract with the onset of opacities at 20–40 years
  - Fundus:

    optically empty vitreous cavity
    liquefied vitreous with fibrillar condensations and mobile filaments
    equatorial and perivascular lattice changes
    clogged peripheral vessels; pigmentation spots in the periphery
    atrophy of the RPE without retinal detachment

- Management:
  - genetic counseling
  - crystallin extraction

Jansen Syndrome

- AD
- It is Wagner syndrome associated with retinal detachment.

Stickler Syndrome

- It is a collagenosis with progressive arthro-ophthalmopathy, similar to Wagner syndrome, associated with severe myopia and marfanoid habitus
- AD, chromosome 1q21, 6p21, 12q13
- Ocular:
  - non-progressive high myopia, > 8 D
  - presenile cataract
  - ectopic lens
  - glaucoma
  - Fundus:

    optically empty vitreous cavity, with circumferential equatorial membranes
    radial palisade degeneration, with vascular sclerosis (lattice radiar)
    retinal detachment with giant tear (frequent), sometimes bilateral

- Systemic:

  - orofacial anomalies—Pierre Robin, with flattened facies and cleft palate, maxillary hypoplasia
  - marfanoid habitus
  - hearing loss
  - mitral valve prolapse
  - abnormal joints with hyperextensibility, arthritis
- ERG—decreases wave *b*.

Familial Exudative Vitreoretinopathy

- AD, rare AR, XLR.
- Onset in childhood.
- Fundus—vitreous degeneration, peripheral temporal fibrovascular line.
- Complications:
  - macular traction
  - tractional retinal detachment
- Management—photocoagulation, cryotherapy and vitreoretinal surgery may be useful in some cases.
- The prognosis is reserved.

Other Vitreoretinopathy

- Erosive vitreoretinopathy
- Dominant vascular inflammatory vitreoretinopathy
- "Snowballs" degeneration

Peripheral Retinal Degenerations

- Retinal degenerations can be [21, 22]:
  - BENIGN

    white with/without pressure
    "cobblestone" degeneration
    peripheral microcystic degeneration
    senile degenerative retinoschisis
  - Predisposing to retinal detachment

    "snail trail" degeneration

lattice degeneracy
zonuloretinal traction "in tuft"
"snowflake" degeneration

Benign Retinal Degenerations

White With/Without Pressure

- The degenerative lesion is located in the periphery of the retina.
- It affects young, black, hyperpigmented and myopic individuals.
- It has NO pathological significance
- Rarely, it can be accompanied by a retinal tear
- White with pressure is visible only with scleral indentation
- White without pressure is visible without scleral indentation.

"Pavingstone" Degeneration

- The incidence of the condition increases with age and is associated with the presence of myopia.
- It is not symptomatic and has no complications.
- It does not require treatment.

Peripheral Microcystic Degeneration

- Intraretinal cysts are present posterior to the ora serrata, outside the plexiform layer.
- These cysts can coalesce and progress to a degenerative lesion—retinoschisis, without increasing the risk of retinal detachment.
- It does not require treatment.

Degenerative Retinoschisis

- Acquired retinoschisis occurs as a result of a degenerative process that consists in the separation of the retina, between the inner nuclear layer and the outer plexiform layer [16].
- *Acquired retinoschisis*
  - Affects 4–7%of the general population and is present in patients over 40 years of age, is bilateral in up to 70% of cases, often symmetrical and frequently associated with hypermetropia

- it is asymptomatic and non-progressive, but may have visual field defects
- is located in an area of peripheral cystoid degeneration in the infero-temporal sector (70%), with vascular occlusions and sclerotic vessels in the periphery
- complications:

  internal (small, round, which can cause retinal detachment) or external (rare, low risk) retinal tears
  rhegmatogenous retinal detachement

- Treatment—surgical, only in the presence of rhegmatogenous retinal detachment

- *Juvenile retinoschisis*
  - XLR can be present at birth, the chromosome involved is Xp22
  - symptoms:

    it can be asymptomatic
    decreased vision frequently due to vitreous hemorrhage

  - clinical:

    slow progressive evolution
    strabismus, nystagmus
    macular schisis

      with fine radiation from the fovea, macular cysts, and/or prominent foveal microcysts, similar to OMC but without FA changes

    peripheral schist with pigmentation
    vitreous hemorrhage
    specific atrophy in late stages

- ERG—scotopic—selective loss of the *b wave.*
- Absolute CV defect (visual field) corresponding to the location of the retinoschisis.
- Management of juvenile RS:
  - children should limit physical activities because trauma can cause VH (vitreous hemorrhage) and/or RD (retinal detachment)
  - prophylactic treatment is controversial because it may favor RRD
  - if VH occurs, conservative medical treatment is attempted in the child, PPV (*pars plana vitrectomy*) is rarely indicated
  - if RRD occurs it is recommended

    adapted surgical treatment

Retinal Degenerations Predisposing to DR [20, 23]

"Snail Track" Degeneration

- Frequent in myopes, it is considered an early form of lattice.
- Clinical
  - degenerative areas of thinned retina with a circumferential orientation with a glossy appearance, located in the periphery of the retina
  - large, round holes located in the area of the lesion may be present
  - atrophic holes can accentuate the degenerative process and increase the risk of RD.
- Asymptomatic forms with degenerative lesions and atrophic holes do not require prophylactic treatment, unless the patients are:
  - high myopia
  - corneal, crystalline opacities
  - presents with RD in the fellow eye
  - families with RD.
  - Patients with subjective manifestations require prophylactic treatment with laser photocoagulation around the hole.

Lattice Degeneracy

- Bilateral condition, more common in myopes, preferably located supero-temporal
- It is characterized by:
  - oval lesions located between the equator and ora serrata, with thin retina
  - white "lattice" lines crossing with/or without round holes in the area of the lesion, with a circumferential orientation
  - vitreous liquefaction with marginal vitreous adhesion
  - secondary atrophic retinal holes appear
  - retinal breaks at the edge of the injury of some vitreoretinal adhesions
- Management:
  - clinical follow-up of patients with lattice degeneration
  - Prophylactic laser photocoagulation:

    breaks in lattice degeneracy
    patients with rhegmatogenous retinal detachment in the fellow eye
    prophylactic for the patients with retinal detachment with extensive lattice or in the case of retinal breaks located outside the lattice area.

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Chapter 13
Ophtalmological Pathology and Management of Ocular Disease in Retinal Metabolic Phacomatosis

Marieta Dumitrache

Abstract **Amaurosis fugax** is caused by carotid disease (the most common cause of Amaurosis fugax in elderly patients). **Obstruction of the retinal central artery (CRAO)** is an absolute ophthalmological emergency. Treatment need to be institute immediately, local and invasive procedures. **Branch retinal artery occlusion** (the temporal retinal vessels) has clinical signs located in the sector of arterial obstruction. Retinal venous occlusive by obstruction of the **retinal central vein** has two forms: CRVO non-ischemic 75–80% and CRVO ischemic 20–25% associated with severe vision reduction. Current treatment of CRVO requires the use of fibrinolytic agents and antiVEGF medication, panretinal laser photocoagulation by the ischemic territories, treatment of glaucoma. **Diabetic retinopathy DR** is a complication of diabetes, the leading cause of blindness and possible complication: intravitreal hemorrages, fibrovascular membranes, tractional RD, neovascularisation, macular edema. **Diabetic maculopathy** is a most common cause of vision lost in DR. Treatment of DR: intravitreal VEGF, photocoagulation laser, as needed posterior vitrectomy. **Retinopathy of prematurity VRO** is a vasoproliferative retinopathy that occur in premature infants, with evolutions stadial (5). Is necessary prophylaxis by early detection of ROP stage and curative treatment is laser and cryotherapy, vitrectomy with and without lensectomy. **Eales disease** is an obliterative idiopathic, bilateral, asymmetric, retinal, vasculopathy, affecting the peripheral retina in the young adult male. Phacomatosis are hereditary conditions (apart from Sturge-Weber, Wyburg-Masson syndrome). They are characterised by the simultaneous damage to the eye, skin, and CNS.

Keywords Amaurosis fugax · Obstruction of the retinal central artery Obstruction of the retinal central venous · Diabetic retinopathy · AntiVEGF · VRO · Sturge-Weber · Phacomatosis

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Disease Retina Vascular

Amaurosis fugax

- It is the transient, sudden loss of unilateral vision (due to insufficient perfusion) in the retinal ophthalmic circulation (CRA) choroidal and/or optic nerve (posterior ciliary arteries) with a short duration, seconds, minutes [1, 2].
- Amaurosis fugax is caused by:
  - ocular—GPUD, transient increase in IOP, Horton temporal arteritis, ON drusen, PVD, orbital hemangioma, orbital osteoma, incomplete retinal vascular occlusion, HTA
  - vascular—carotid diseases, carotid stenosis, heart diseases
  - neurological—papillary edema, optic neuritis, migraine, intracerebral tumors, pseudotumor.
- Symptom
  - temporary loss or decrease of vision, with return to normal VA, **total or sectorial.**
  - **outside of the incident, VA is normal.**
- Fundus—normal or signs of other pre-existing vascular conditions.
- Carotid diseases are the most common cause of amaurosis fugitive and monocular blindness in elderly patients [3].

Treatment
- finding the cause
- periodic interdisciplinary control (Internal Medicine, Neurology, ophthalmologist).

Retinal Arterial Occlusion: RAO

- RAO is the arterial obstruction involving the CRA or one of the branches, produced by embolus or thrombosis associated with vascular spasm; in the end, serious retinal ischemia occurs because the retinal vessels are terminal without supplementary collateral circulation; the consequence of ischemia is the sudden, total, and permanent decrease in VA.
- RAO is
  - central retinal artery occlusion CRAO
- Etiologically, RAO is produced by:
  - thrombosis related to atherosclerosis at the level of the lamina cribosa
  - carotid embolism—cholesterol, fibrino-platelet, calcium plaques

  - cardiac emboli—calcium, thrombi, myxomatous material
  - periarteritis, arteritis—Horton's disease (rare), SLE, Wegener's, polyarthritis nodosa, scleroderma
  - retinal migraine
  - angiospasm (rare)

- RAO is more common in men, unilateral, rarely (1–2%) bilateral.

Obstruction of the Central Retinal Artery

- CRAO is an absolute ophthalmological emergency because the retinal circulation it is terminal, without collaterals, and total retinal ischemia is definitive [4, 5].
- The obstruction is frequently produced at the level of the lamina cribrosa, by atherosclerotic and sometimes calcium embolus.
- Causes of RAO:
  - general causes—are the most common:

    embolism:

    is the main cause of retinal vascular obstructions;
    most frequently occurs in: atherosclerosis, hypercholesterolemia, cardiac myxoma, valvulopathies, endocarditis, fractures, trauma;

    thrombosis on a vessel with damage to the venous wall:

    inflammatory arteritis in: Horton's disease, collagen diseases - SLE, periarteritis nodosa, Takayasu's disease, Churg-Strauss syndrome;

    hypercoagulability: polycythemia, antiphospholipid syndrome
    infectious arteritis: syphilis, leptospirosis, HIV

  - local causes—rare

    OCULAR

    inflammation in: toxoplasmosis, acute retinal necrosis syndrome
    papillary drusen
    arterial macroaneurysm

    orbit: cellulitis, tumors, RB (retrobulbar) hematoma, **RB injection**, trauma**The major risk factor for OACR is atheroma and embolic cardiac abnormalities.**

- Symptoms
  - total decrease in VA to light perception, unilateral, sudden, painless

    if the cilioretinal artery originating in the ciliary arteries is present, macular ischemia is less profound and VA less decreased (20%)

if the cilio-retinal artery originates in the CRA, the VA is profoundly decreased

- amaurotic mydriasis, simultaneously with VA decrease
- DPAR
- Visual field with major deficit or absent

- Clinical signs
  - There are signs of retinal ischemia through vascular obstruction
  - Fundus

    whitish diffuse retinal edema, suddenly installed 15′ after the occlusion, permanent ischemic **lesions occur 90′ after the obstruction**
    thin arteries, with segmentation of blood flow and/or interruption of circulation in the obstructed arteries
    if there is a cilioretinal artery, the territory served by it (interpapillomacular), remains normal, but is surrounded by retinal edema
    normal veins, sometimes segmented blood column
    cherry red macula by the contrast between the macula alba and the colored foveola, without edema
    resorption of retinal edema after several weeks with optic atrophy.

  - risk of bilateralization of CRAO—10%
  - complete clinical examination, internal medicine, cardiology, cardiac ultrasound is mandatory
  - laboratory examination: ESR, CRP, blood glucose, coagulogram, lipid profile, antiphospholipid, anticardiolipid, antinuclear antibodies, rheumatoid factor, lupus cells, etc.
  - cardiac assessment (EKG, Holter, Doppler)
  - neurological examination if needed
  - visual field, FA, OCT

Positive diagnosis

- Symptoms—unilateral, painless, sudden vision loss
- Eye signs [6–8]
  - areflexive mydriasis with consensual reflex present
  - normal anterior pole
  - Normal IOP
  - Fundus

    in the first hours the fundus can be normal
    arteries of reduced caliber
    milky white ischemic retinal edema
    cherry tomato macula
    sometimes visible embolus at the arteriovenous junction
    if the cilioretinal artery is present (in 25% of cases) the interpapillomacular territory is perfused and better VA

- Differential diagnosis [9–11]
  - occlusion of the ophthalmic artery with VA decrease, without cherry red macula
  - NOIA—A (anterior ischemic arteritic optic neuritis)—if GCA, this may produce CRAO and requires steroid treatment to protect the second eye
  - sphingolipidosis—Tay-Sachs, Niemenn-Pick.

Treatment

- The treatment is an absolute emergency and must be instituted immediately after establishing the positive diagnosis of the eye disease, because if the arterial obstruction exceeds 90 min, visual recovery is no longer possible [12–14];
- Multidisciplinary approach, with special attention to the cardiovascular and cerebrovascular systems.
- Local treatment [15, 16]
  - eye massage: direct pressure is applied for 5–15 s, then released. It is repeated several times. A posterior pole lens or digital massage can be used. Eye massage can dislodge the embolus in the arterial circulation and improve retinal perfusion.
  - hyperbaric oxygen (HBO) therapy
  - carbogenic inhalation therapy
  - reduction of intraocular pressure (with systemic or local agents)
  - anticoagulant therapy
  - sublingual isosorbide therapy
  - systemic steroid therapy. The purpose of each is to increase blood flow and the concentration of oxygen in the blood.
- Invasive procedures [17–20]
  - anterior chamber paracentesis
  - decrease in IOP
  - laser embolectomy
  - pars plana vitrectomy
  - intra-arterial thrombolysis [21, 22].
- ***Anterior chamber paracentesis***
- **Drug reduction of intraocular pressure**: acetazolamide 500 mg iv or 500 mg orally can be given for immediate reduction of intraocular pressure. Topical medication is also used to reduce intraocular pressure [23].
- **Laser embolectomy**: the lysis of emboli can be performed with the 1064 nm photodisruptive Nd:YAG laser [14, 24].
- **Vitrectomy via pars plana (VPP) with direct central retinal artery massage**
- **Intra-arterial fibrinolysis** [25]
- Systemic complications of fibrinolytic therapy include: transient ischemic attack (TIA), stroke, intracerebral hemorrhage, and hematoma.
- Treatment of associated diseases: hypertension, diabetes, carotid disease, GCA.

OACR with Cilioretinal Artery Present

- The cilioretinal artery provides macular irrigation with preservation of central vision in the eye with CRA obstruction [26].
- Fundus shows a normal-appearing retinal island temporally localized to the papilla surrounded by thickened white (milky) edematous retina.

Branch Retinal Artery Occlusion

- Branch retinal arterial occlusion occurs at the bifurcation of the artery, because at this level the vascular lumen narrows. **In 90%** of retinal arterial branch occlusion cases, **the temporal retinal vessels are involved** [27, 28].
- Etiologically, it is more often embolic and sometimes periarteritic with obstruction at the bifurcation of the CRA and obstruction of the superior temporal branch with macula involvement.
- The occlusive episode may be preceded by amaurosis fugax.
- The sudden decrease in VA is much less depending on the location of the obstruction, but it is important if the obstruction is in the superior temporal branch.
- Clinical signs—located in the sector of arterial obstruction
  - filiform artery, with segmental circulation
  - sectorial retinal edema
  - soft exudates.
- Visual prognosis—better than RAO.
- Treatment
  - anterior chamber puncture
  - acetazolamide iv, mannitol
- **These patients are at increased risk of stroke or repeat occlusion, which is why they must be monitored interdisciplinary**.

Cycloretinal Artery Occlusion (Very Rare)

- It can be isolated or associated with CRAO, NOIA in Horton's disease.
- Symptoms—sudden drop in central VA
- Clinical signs—localized retinal edema (interpapillomacular).

Ophthalmic Artery Occlusion

- Total VA decrease (nlp) present in mucormycosis.

Ocular Ischemic Syndrome

- It is chronic ocular hypoperfusion secondary to severe atherosclerotic homolateral carotid stenosis [29].
- Ischemia of the anterior and posterior segment of the eye is caused by ipsilateral carotid occlusive disease (rarely ipsilateral ophthalmic artery obstruction), carotid dissection, arteritis (rare) [30, 31]
  - affects patients aged 50–70 years, unilateral in 80% of cases, more often men (2:1)
  - **50% of patients have complete obstruction of the ipsilateral carotid artery**
  - it is associated with atheromatosis, HTA, diabetes, cerebrovascular accident, peripheral arterial diseases, ischemic heart diseases [32].
- Symptoms:
  - progressive decrease in vision associated with eye pain and headache (40%)
  - a history of recurrent amaurosis fugax sometimes associated with orbital pain
  - slow recovery of vision after exposure to bright light, due to decreased regenerative power of photoreceptors
- Clinical signs:
  - Anterior pole:

    conjunctival and episcleral hyperemia
    corneal edema and striae
    precipitates absent but Tyndall + by ischemic iritis
    iris atrophy, rubeosis iridis
    without posterior synechiae
    intraocular hypertension may be present
    cataract
    slowly reactive semimydriatic pupil

  - Fundus:

    cystoid macular edema, cherry macula
    disc edema
    exudates
    cotton wool spots
    thinned retinal arteries, spontaneous arterial pulsations
    dilated veins without tortuosity
    retinal hemorrhages, microaneurysms
- Differential diagnosis:
  - CRV occlusion nonischemic form
  - stasis venous retinopathy
  - diabetic retinopathy
  - parafoveal telangiectasia

  - radiation retinopathy
  - Takayaso's disease

- Cardiovascular monitoring is required with full assessment of carotid patency including Doppler ultrasound exploration, including carotid angiography if Doppler is inconclusive; these scans show ≥90% carotid obstruction
- Treatment:
  - 500 μm spot panretinal laser photocoagulation to limit the development of anterior and posterior segment neovascularization
  - carotid endarterectomy if there is carotid obstruction, which must be performed to be beneficial before rubeosis iridis develops
  - treatment of increased intraocular pressure if necessary
  - antiglaucomatous interventions when gonioscopically the angle of the anterior chamber is closed
- Prognosis [33]:
  - Reserved, with possible death (5%) in cardiovascular diseases
  - Vision decline to cf. within 1 year, faster if associated with rubeosis iridis.
- Treatment of associated diseases:
  - diabetes
  - hypertension
  - corticosteroid therapy in GCA
  - endarterectomy in carotid disease.

Retinal Venous Occlusive Disease

- Retinal venous occlusions (RVO) constitute a group of frequently encountered conditions, being the second cause of severe visual impairment after diabetic retinopathy within retinal vascular pathology [10].
- In RVO, the decrease in vision is not great, therefore the eye disease can be diagnosed late due to complications: secondary glaucoma, vitreous hemorrhage, proliferative retinitis.
- **CRVO the non-ischemic form** of CRVO (obstruction of the central retinal vein in 75–80% of patients).
  - neovascularization is rare (2% incidence), but conversion to the ischemic form is relatively common.
- **CRVO ischemic form** is associated with severe vision reduction:
  - it affects 20–25% of CRVO patients
  - it is complicated with neovascular glaucoma by the neovascularization of the anterior segment—rubeosis iridis, which induces the appearance of secondary neovascular glaucoma [29].

  - associated posterior segment neovascularization may cause hemorrhage vitreous and consecutive retinal detachments, through fibrinous blood rearrangements.
  - **Complications:** macular edema, iris/retinal disc neovascularization secondary to retinal ischemia [34]

- The causes of RVO [35] ocular and general, allow the formation of thrombus in the vein by:
  - CRV compression of rigid CRA in atherosclerosis in arterio/venous junctions
  - inflammatory degenerative diseases of the venous wall
  - vasculitis: sarcoidosis, syphilis
  - oral contraceptives
  - blood dyscrasias, exophthalmos, hypertension
  - arteriosclerosis with hyperlipidemia
  - diabetes, HTA
  - hyperviscosity, macroglobulinemia, multiple myeloma
  - other causes: TSC, orbital thrombosis, Coats, von Hippel, Eales disease, retinal phlebitis.

- Risk factors [8, 36]:
  - Eye: retinal periphlebitis, ocular hypertonia
  - Systemic: diabetes, hypertension, hyperlipidemia, hyperviscosity, sarcoidosis, SLE, oral contraceptives, coagulation abnormalities, autoimmune diseases, multiple myeloma

- **OVCR** manifests itself in two forms [4, 5]:
  - edematous capillaropathy
  - ischemic capillaropathy, without a clear demarcation between these two forms.

- **Oedematous capillaropathy**—perfused non-ischemic, milder:
  - is more common (70%)
  - symptoms

    variable VA decrease, unilateral, in one white, painless eye
    Relatively preserved VA > 1/10
    minimal visual fields deficits with enlargement of the blind spot, central scotoma.

  - Fundus [18]

    tortuous dilated veins
    superficial hemorrhages in flames along the vessels, punctate, arranged up to the periphery of the retina, deep hemorrhages rare
    normal arteries, cotton wool spots
    diffuse retinal edema (dark gray retina), disc edema
    very rarely preretinal and/or prepapillary neovascularisation, intravitreal hemorrhages

- anterior pole exam may show rubeosis iris, HIO
- complementary exams

  blood glucose, lipid balance, electrophoresis, leukocyte formula
  internal medicine exam (hypertension, diabetes for risk factors)
  FA for differential diagnosis, to highlight neovessels or macular ischemia
  OCT for the quantification of macular edema.

- evolution

  favorable, uncomplicated with resolution in 6–12 months, 50%
  or evolution towards the ischemic form 16%

- complications

  cystoid macular edema with evolution to pseudohole and macular hole
  careful examination of the other eye
  differential diagnosis

    hypertensive retinopathy, diabetes (bilateral)
    carotid stenosis with chronic ocular ischemia
    papilledema and intracranial hypertension

• Ischemic capillaropathy—non-perfused

- rare, but functional signs are severe
- onset with significant decrease in unilateral VA
- symptoms:

  important drop in VA
  DPAR present
  Visual field—central and peripheral deficits
  clinical signs
  the same signs as in the edematous form, but more severe
  Fundus

    irregular, dilated, tortuous veins
    filiform arteries
    abundant, dense hemorrhages with variable aspects (flame, large, punctate), superficial, deep
    inconstant associated signs
    papillary ± macular edema
    papilla covered with hemorrhages and exudates
    dense confluent cotton wool spots located preferentially in this interpapillomacular form
    collateral circulation, preretinal and/or prepapillary neovessels, intravitreal hemorrhages

- signs of gravity

  VA—cf.
  Rubeosis iridis (at the edge of the pupil, in the iridocorneal angle)

secondary neovascular glaucoma
Fundus—many cotton wool spots, interpapillomacular, deep round hemorrhages

- Evolution

  macular epiretinal gliosis and pigmentary changes (sometimes)
  rubeosis iridis in 2–4 months (50%) **90-day glaucoma**
  rubeosis iridis and neovascular glaucoma in 50% of cases

- prognosis—reserved in macular ischemia

Differential diagnosis
- RD
- retinopathy from severe arterial hypertension
- retinopathy from blood diseases
- retinopathy in hematological diseases

Branch Retinal Vein Occlusion/BRVO

- It occurs at arteriovenous junctions by compression of the vein by the artery with rigid walls [37].
- The temporal branches are the first to be affected (60%) superotemporally.
- Symptoms—are minimal in peripheral forms (or absent) are present in macular damage with reduced vision, metamorphopsia.
- Clinical signs—fundus appearance in the CRVO, but in the obstructed sector.
- Complications:
  - OMC, NVE, retinal and macular gliosis.
- Treatment—laser photocoagulation after FA.

Hemiretinal Vein Occlusion

- Onset with altitudinal visual field amputation and variable VA drop.
- Frequently affects the inferior or superior hemiretina.
- Prognosis depends on macular edema and ischemia.

Venous Stasis Retinopathy

- There are retinal vein obstructions, associated with occlusive diseases of the carotid artery.
- Patients 30–40 years old, with diabetes, hypertension, carotid disease, under oral contraceptives (with estrogens).

- Symptoms:
  - variable depending on the location of the obstruction
  - VA decreases if the macula is affected
  - Scotomes on Amsler test, widening of the blind spot
- Fundus
  - dilated, tortuous retinal veins with hemorrhages.
  - papillary edema, sometimes macular (inconspicuous).
- Treatment
  - Anticoagulants are not indicated
  - If VA is low, systemic corticosteroids 0.5–1 mg/day.

Papillophlebitis

- It is CRVO in young people under 40 years of age
- Onset around 50 years, with a sudden decrease in vision more pronounced upon waking, with VA around 2/10.
- The cause is a congenital anomaly of the optic disc that causes compression of the CRV at the level of the lamina cribrosa
- Moderate CRVO with papilledema.
- Prognosis - good.

Treatment in CRVO

- Treatment in RVO requires:
  - identification of risk factors, their medical treatment and treatment of RVO complications [37–39]
  - Investigation of signs of severity in the presence of an ischemic form:

    VA;
    rubeosis iridis on the edge of the pupil, biomicroscopy in the iridocorneal angle;
    IOP measurement;

  - Fundus: numerous deep hemorrhages, interpapillomacular cotton wool spots.
  - Examination of the eye which may show signs of: malignant hypertensive retinopathy, diabetes (bilateral); chronic ocular ischemia in carotid stenosis; papillary edema in ICHT (intracranial hypertension); radical retinopathy [40].

Current treatment of OVR requires the use of anticoagulants, fibrinolytic agents and anti-VEGF medication that have shown benefits in the treatment of RVO [11, 41].

CRVO

- Tissue plasminogen activator (TPA), corticosteroids, bevacizumab (Avastin).
- Also administered: coumarin anticoagulants (warfarin) and other drugs: urokinase, troxerutin, ticlopidine, pentoxifylline.
- Hemodilution.
- Panphotocoagulation, macular grid.
- Surgical: radial optic neurotomy.

BRVO (branch retinal vein occlusion) [42]

- Corticosteroids, Avastin.
- Photocoagulation, macular grid.
- Surgical incision of the common arteriovenous sheath.

Corticosteroids [40]

- They improve VA by reducing macular edema [26].
- Intravitreal injection of triamcinolone acetonide 1 mg (4 mg dose) is used for the treatment of associated OMC.

Bevacizumab

- Bevacizumab (Avastin) is a human monoclonal antibody directed against all VEGF isomers that is administered intravenously in the treatment of colorectal cancer [43–45].
- Administered intravitreally, bevacizumab causes a decrease in macular edema approximately one week after administration (documented by OCT) and an improvement in visual function [10, 39, 41, 46].
- Intravitreal injection of bevacizumab 1.25 mg repeated every 1 month reduces macular edema.
- Anti-VEGF therapy is indicated in:
  - neovascular glaucoma
  - macular edema.
- It is performed by intravitreal injection of bevacizumab.
- A significant improvement in vision and a significant reduction in retinal thickness is noted with OCT compared to other treatments.

Tissue plasminogen activator: TPA

- TPA converts plasminogen to plasmin and destabilizes intravascular thrombi [47].
- In CRVO, TPA can be administered:
  - systemic—50 µg (risk of intracranial hemorrhage).
  - intravitreal 65–110 µg in recent forms, with possible stabilization in 70% of cases.

    lower risk of systemic complications.
    exhibits retinal toxicity.
  - endovascular cannulation of retinal vessels with injection directly into the occluded vein after pars plana vitrectomy (risk of vitreous hemorrhage).

- Complications:
  - vitreous hemorrhage.
  - retinal detachment.
- Prophylactic treatment of associated conditions:
  - Diabetes, hypertension, atherosclerosis, control and treatment of underlying disease and risk factors
  - reduction of hematocrit to 35–38% by hemodilution.
- Systemic medical treatment
  - interdisciplinary control to detect causal factors.
  - control and treatment of underlying disease and risk factors
- Ophthalmological treatment [4, 5]:
  - Lowering intraocular pressure if it is elevated.
  - Neovascular glaucoma (100 days).

    preventing it if it is detected in time by:
    systematic slit-lamp examination to highlight new vessels on the iris.
    gonioscopy examination to highlight neovascularization in the angle.
  - Emergency retinal pan photocoagulation in iris rubeosis and angular neovascularization.
- Urokinase
  - Infused through the microcatheter, a VA improvement was found after this fibrinolytic.
- Troxerutin
- Ticlopidine
- Pentoxifylline
  - administered orally or by infusion, relieves VA in some patients with RVO.

Hemodilution

- Thus, reducing hematocrit by hemodilution decreases plasma viscosity and may improve microcirculation and retinal perfusion.
- Adverse effects may occur (lethargy, fainting, dyspnea).

Surgical treatment [48–50]

- Endovascular retinal surgery (in CRVO) with plasminogen activator injection.
- Vitrectomy if needed.
- Radial optic neurotomy.
- Arteriovenous junction adventitial dissection—sheatotomy.
- Vitrectomy with or without sheathotomy for macular edema improves long-term vision.

CRVO Laser Treatment [51]

- *Treatment of RVO Non-Ischemic Form*

Panretinal laser photocoagulation by which the ischemic territories are destroyed, to prevent the development of preretinal, papillary and iris neovascularization in ischemic CRVO is indicated in major ischemic forms that are serious and rapidly complicated with iris neovascularization and GNV that can be systematically prevented by pan retinal FC [51].

- If there is NVR or secondary anterior segment RVO, pan retinal FC should be initiated rapidly to reduce intravitreal hemorrhage and avoid neovascular glaucoma.

Macular photocoagulation
- **Focal FC** can be used in macular edema secondary to RVO, but is less effective than antiVEGF medication or dexamethasone implant [51]
- is indicated in venous branch obstruction more recent than 3 months, complicated with persistent macular edema.
- allows cystoid macular edema regression and VA stabilization and should not be performed before three months because spontaneous regression is possible in many cases with OMC.

Treatment of GNV if it has set in is urgently indicated panretinal FC, after lowering the IOP by local hypotonic treatment and acetazolamide orally, IV or surgical treatment in severe cases.

Treatment of branch retinal vein obstruction
- Treatment of risk factors.
– Sectorial photocoagulation for the treatment of ischemia in obstructed territory, to prevent the development of a vitreous hemorrhage through preretinal neovascularization.
– Macular photocoagulation is indicated in branch obstruction more recent than 3 months, complicated by persistent macular edema, with VA less than 5/10, which allows stabilization and improvement of VA.

FC laser Pascal, with the application of numerous impacts (up to 25) in fractions of a second, with short pulse duration, of high power through cumulative energy.

Thanks to the short duration of the laser impacts, the pascal photocoagulator induces a harmless thermal effect, decreases the treatment time, improves the patient's comfort [7].

- **OVCR treatment** by laser FC (depending on FA) clearly improves the visual prognosis, FC also being an efficient treatment of the complications of ischemic capillaropathy.
- Laser FC in the treatment of OVCR provides prophylactic therapy of complications and can improve the prognosis of venous occlusion.

FC in OVCR is effective, improves prognosis, limits complications, but must be applied and indicated with discernment.

The nonischemic form

- Anticoagulants—they are not effective.
- Fibrinolytics—by injection into the ophthalmic artery, difficult to apply, with risks of complications (not used).
- Isovolemic hemodilution in the first months after the onset of the disease, with a decrease in blood viscosity and improvement in retinal circulation; can be effective.
  - May be indicated in CRVO, without extensive peripheral ischemia, less than one month after onset, in the absence of complications.
- Intravitreal triamcinolone acetonide injection 1–4 mg—Kenacord or dexamethasone-based implant 0.7 mg—Ozurdex, would reduce macular edema in many cases, but requires repeated injections indefinitely and can be complicated with cataracts and glaucoma (complications of corticotherapy).
  - Corticosteroids decrease vascular permeability and decrease VEGF expression *in vitro.*
  - Therapeutic efficiency is fast, transient and requires repeating the treatment.
- In all cases of RVO, the non-ischemic form requires clinical surveillance and FA for several months for the early detection of the transition to the ischemic form [4].
  - ***Vitreoretinal surgery*** in the treatment of RVO has as its objective either the treatment of the venous occlusion itself or of the secondary macular edema.
  - **OVR treatment**.

Ischemic form

- Partially benefit from the treatment of nonischemic forms of OVR: medical treatment is ineffective, isovolemic hemodilution is little effective.
- Intraocular corticosteroid injection.
- **Intravitreal injection with anti-VEGF is the basic treatment of macular edema post-CRVO, with VA less than 6/10, with:** ranibizumab, aflibercept, repeated bevacizumab [5, 23, 52].
- Laser photocoagulation treatment is indicated depending on the clinical form, evolution, and complications of RVO.
  - FC laser consists of applying the laser beam to the retina to produce a therapeutic burn in a selected area and is indicated for the treatment of exudative ischemic areas with neovascular proliferation.
  - Focal FC may be useful in some macular edemas, being indicated in venous branch obstruction, with OCT evaluation.

- is very useful in macroaneurysms where direct FC helps their regression.
  - Panretinal FC is indicated in retinal and anterior segment neovascularization, in areas of extensive nonperfusion to FA.
  - FA, OCT, VA control.
- **Photocoagulation treatment does not restore vision but prevents GNV.**
- **Laser treatment must be preceded by intravitreal injection of antiVEGF and allows regression of new vessels and retinal edema.**

Treatment of RVO in patients with macular edema, with foveal damage [9, 23, 53].

- Anti-VEGF intraocular injection (ranibizumab, aflibercept, bevacizumab), triamcinolone intraocular injection, dexamethasone implant.
- FC can be used in secondary macular edema, retinal vein branch obstruction, but is less effective than antiVEGF drugs.

Hypertensive Retinopathy: RH

- Represents fundus changes in patients with systemic HTA.
- Hypertensive retinopathy (RH) is a disease characterized by retinal degeneration induced by HTA in relation to the duration and severity of HTA, chronic evolution, and age of the patient.
- Hypertensive retinopathy represents retinal vascular changes secondary to a prolonged increase in systemic arterial pressure.
- The primary response of the arterioles in HTA is narrowing of the vascular caliber, dependent on the presence, location, and degree of involutional vascular sclerosis by fibrosis.
- Arterial hypertension—is the systemic increase in BP above 140/90 on at least three different determinations.
- Hypertensive retinopathy in elderly people is caused by [4, 5]:
  - vasoconstriction of retinal arteries in direct correlation with the degree of HTA (rare in young people, common in elderly people due to involutional sclerosis)
  - retinal arteriosclerotic changes present after 60 years:

    arteries with reduced caliber, diffuse, generalized or localized with arteries with a filiform or moniliform appearance.
    parietal arteriolar reflex change with metallic appearance with “copper wire” (orange yellow) or “silver wire” (white) arteries
    modification of the arteriolar path with rectilinear, rigid, tortuous arterioles.
    arteriovenous junctions with crossing changes (due to common adventitial sheath between artery and vein)

The stiff-walled artery produces compression of the vein with its changes and constitutes **the Salus-Gunn sign.**
The Salus-Gunn sign has three stages.

Stage 1—narrowing of the venous caliber at the crossing.
Stage 2—change in venous caliber at the crossing and deviation of the vessel with its dilation upstream of the crossing.
Stage 3—prethrombosis with the appearance of small hemorrhages at the level of the crossing area.

Severe HTN can lead to obstruction of the precapillary arterioles and the development of cotton wool spots.

- **arteriosclerotic changes are irreversible and do not disappear with the treatment of hypertension**.
- **stagnation of the blood column with increased vascular permeability through hypoxia**, favors the production of retinal hemorrhages in flame, hard exudates, retinal edema.

ON head edema is secondary to malignant hypertension
exudate deposits in the fovea in Henle's layer can lead to macular star.

- Hypertensive retinopathy can be associated with other eye pathologies.
  - arterial, retinal venous occlusion
  - AION
  - oculomotor paralysis
  - retinal arterial macroaneurysms.
- **The signs of hypertensive retinopathy** are [14]:
  - *before breaking the blood-retinal barrier*

    segmental arterial vasoconstriction, single or multiple, may disappear when blood pressure normalizes in young people.
    arterial vasodilatation, passive to the persistence of arterial hypertension

  - *after breaking the blood-retinal barrier*

    multiple, superficial, linear, flaming hemorrhages located in the layer of nerve fibers. Deep, denser, round hemorrhages reflect retinal ischemia. After the therapeutic lowering of the hypertension, the hemorrhages disappear in a few weeks.
    cottony nodules (soft exudates, dysoric nodules) small, white, shiny, with blurred, superficial edges, located in the vicinity of areas of ischemia, near vessels, in the posterior pole and respecting the macula.
    dry exudates appear as white or yellow spots, well-defined and located in the posterior pole, behind the retinal vessels, with a radial disposition, centering the fovea and constituting the macular star.
    papillary edema—requires urgent treatment of hypertension.

- initially minimal edema of the papilla, with a slightly shiny papilla with venous dilatations and diminution of the spontaneous venous pulse
- in evolution the papillary edema increases, the papilla is surrounded by superficial hemorrhages in the flame, cotton wool spots and sometimes choroidal folds.

  Acute choriocapillary occlusion syndrome—in patients with malignant hypertension, when their vessels are not sclerotic but flexible (hypertension of toxic origin, toxemia of pregnancy).

- Clinical—subretinal yellow spots grouped or disseminated and often associated with a serous detachment of the retina (peripheral or in the posterior pole) with sequelae lesions, Elsching spots appearing 2–3 weeks after hypertensive pustule. These are small pale, round spots, centered by a deep pigment point, located in the vicinity of the papilla or in the periphery.

- Vascular changes in hypertension are bilateral, symmetrical, asymptomatic; decreased vision may rarely be present.
- **Risk factors for hypertension:**
  - age (men >55 years, women >65 years)
  - race—2 times more common in African Americans
  - hyperlipidemia—cholesterol >250 mg/dl
  - diabetes
  - smoking
  - abdominal obesity
  - sedentariness
  - cardiovascular disease in young people
- Ocular changes in hypertension are in the retina, choroid, optic nerve [41]
  - Retina:

    arterial changes

    color—bright arterial reflex
    path—rigid, rectilinear arteries
    caliber—diffuse, generalized arterial narrowing.

    venous changes (smaller)

    color—dark veins with a metallic appearance
    path—veins compressed by the rigid artery at the crossing point.

    ophthalmoscopic changes

    edema, hemorrhages

  - Choroid

    detachment of the retina in the form of subretinal yellow spots,
    Elsching spots with RPE reshuffle

– Papilla

Papilledema in malignant hypertension
Bilateral peripapillary retinal hemorrhages and exudates
Ischemic optic neuropathy

Keith-Wagener Barker Classification [10]

Stage 1: Hypertensive angiopathy
- narrowed arterioles with widened parietal reflex with "copper wire" appearance.
– vascular tortuosity
– Salus Gunn sign 1—compressed and narrowed vein at the arterial -venous junction

Stage 2: Hypertensive angiosclerosis
- minimal generalized reduction of arteriolar caliber especially of small branches
– generalized arterial constriction associated with cross-vein deviation.
– stiff arterioles with a "silver wire" appearance
– dilated and tortuous veins
– Salus Gunn sign 2—change in venous caliber and change in veins trajectory (in bayonet)

Stage 3: Hypertensive retinopathy
- stage 2 arteriovenous changes
– chorioretinal angiosclerosis
– prethrombosis with small crossover bleeds
– superficial, deep retinal hemorrhages
– soft (cottony) exudates
– hard perimacular exudates in star macula
– retinal edema

Stage 4: Retinal neuroretinopathy
- changes stage 3
– papillary edema

The defect of this classification is the mixing of signs of arteriosclerosis with those produced by hypertension, choroidal alterations being ignored.

Cyclic Forms of Hypertensive Retinopathy
- with senile vascular sclerosis in patients over 60 with signs of advanced arteriosclerosis
- without vascular sclerosis in younger individuals with elastic arterioles subject to short-term BP elevation

  – arterioles with vasoconstriction
  – minimal cross marks (absent)
  – occasional small hemorrhages
  – without exudates

- with compensatory arteriolar sclerosis in patients with prolonged hypertension, with minimal or absent arteriosclerosis associated with edematous or renal retinopathy.
- Malignant hypertension with abundant cottony hemorrhages and exudates

Differential diagnosis

- non proliferative diabetic retinopathy with dot hemorrhages, microaneurysms, hard perivascular exudates, absence of the Salus-Gunn sign.
  - CRVO
  - retinopathy from anemia where Roth spots are present, signs of arteriosclerosis and hard exudates are absent.
  - leukemic retinopathy
  - collagen vascular diseases—may have cotton wool spots, retinal hemorrhages, but no signs of arteriosclerosis.
  - differential diagnosis of papillary edema with stasis, papillitis, NOIA

Complications [54]

- vascular by CRAO, TVCR, AION with irreversible reduction (loss) of vision
  - vitreous hemorrhages
  - oculomotor paralysis by stroke

Treatment [21]

- careful eye, cardiovascular, cerebrovascular medical consultation
  - hypertension treatment

Hypertensive Retinopathy in Pregnancy: Pregnancy Toxemia

- It is characterized by increased BP, proteinuria, and generalized edema.
  - BP increases above 160/100 mmHg → 200/300 mmHg.
  - narrowing of arterioles (initially nasal, then total)
  - persistent vascular spasm produces retinal ischemia with cotton wool spots, superficial hemorrhages, and rapid progression of retinopathy with edema and exudation, macular star, rarely bilateral exudative RD (spontaneously reattached).
- Changes from retinopathy are reversible and disappear after tension stabilization; if it is necessary to save the life of the patient and the child, sometimes even termination of pregnancy is necessary.

Diabetic Retinopathy: DR

- Diabetic retinopathy is a complication of diabetes and is the leading cause of blindness in diabetic patients aged 20–65 years.
- Pathogenic DR is produced by:

- **Microvascular occlusion** with increased vascular permeability and increased platelet adhesiveness, the consequences are:

  obstruction of blood capillaries and the appearance of nonperfusion areas
  vascular anomalies
  neovascularization

- **Microvascular diffusion** through the rupture of the blood-retinal barrier with:

  diffuse retinal edema due to excessive capillary diffusion.
  localized retinal edema and deposits of hard exudates by focal diffusion alongside microaneurysms.
  hemorrhages [31, 55]

- Diabetic retinopathy is an ocular microangiopathy that affects the precapillary arterioles, capillaries, venules, and to a lesser extent the larger retinal vessels.
- Retinal capillary changes produce ischemic retinopathy. Retinal ischemia stimulates the production of vascular endothelial growth factor (VEGF) which causes vascular proliferation and the appearance of neo vessels.
- Fibrovascular proliferation exceeds the surface of the retina and invades the posterior hyaloid.
- Proliferative vitreoretinopathy produces multiple complications:
  - preretinal or vitreous hemorrhages due to neoformation vessel ruptures
  - RD by traction or RRD (if traction caused rupture)
  - iris neovascularization with secondary neovascular glaucoma.
- Risk factors
  - Duration of diabetes
  - inadequate metabolic control
  - pregnancy
  - hypertension, hyperlipidemia
  - nephropathies
- Clinical signs in RD are [4, 5]:
  - **microaneurysms**

    Microaneurysms and punctate hemorrhages are present in early nonproliferative DR.
    are localized dilatations of retinal capillaries, appearing as round, red spots 20–100 μm located in the posterior pole (initially temporal to the fovea) that cannot be differentiated from punctate hemorrhages except with FA.
    their number and evolution are elements of the prognosis.

    rare microaneurysms (1–5) in the posterior pole indicate mild retinopathy with a better prognosis.
    explosion in the number of microaneurysms (between two controls) indicates a worsening of the DR.

the evolution of microaneurysms is varied (their disappearance is done by expanding the non-perfusion areas visible at FA).

- **Retinal hemorrhages**

  punctate hemorrhages—they are small red spots, larger than the microaneurysms, next to which they are placed; they can be superficial, deep.
  flame hemorrhages—elongated, oriented in the direction of the nerve fibers, are located near the optic disc and around the temporal vasculature.
  hemorrhages in clusters—grouped, deep, have the appearance of ink stains on a swab with different shades of red; FA are located in capillary non-perfusion areas, or at their edge;
  diffuse hemorrhages—throughout the thickness of the retina (they are common in venous occlusion)
  petaloid hemorrhages—superficial, resemble a chrysanthemum, have large dimensions (1 PD) and are located at the equator.

- **Hard exudates**

  are accumulations of lipids, proteins in the sensory retina
  small, round, yellow spots, located more in the posterior pole, with varied arrangement.
  in evolution they can be resorbed

- **exudates**—cotton wool spots

  are whitish, diffuse spots, located more frequently in the area of the vasculature and are produced by arteriolar obstruction.
  Their presence in large numbers can be an indicator of rapid evolution towards neovascularization.
  they are also present in retinal vascular diseases: DR, hypertension, retinopathy of pregnancy.
  The rapidity of resorption is related to the capillary bed: if it is healthy, after hypertension, the exudates disappear in two months, while in a patient with DR it takes 6 months.

- **Retinal edema**

  It is produced by breaking the blood-retinal barrier, by diffusion from microaneurysms or capillary hyperpermeability.
  In the foveal area it looks like cystoid macular edema.

- **Venous abnormalities** in the form of venous dilations, venous loops or venous beading (successive dilations and narrowing) especially in large vessels.
- **Retinal neovascularization**—which can produce retinal hemorrhages that can be localized: preretinal (small, macular or "swallow's nest") sub-hyaloid, vitreous (with slow resorption and persistent 3–4 months).

- **Fibrous membranes** accompany the neo vessels and extend along the vascular arches or towards the vitreous body; they can be complicated with HV, RD.
- **Tractional RD** should be carefully monitored.
- **Macular edema**

  is the main cause of visual impairment in RD
  it is associated with microaneurysms
  OCT assesses the thickness of the edematous retina

- **Neovascular Glaucoma** by Chamber Angle Blockage by Irian Neovascularization and Fibrous Tissue.

DR Classification [9]

- **NON-PROLIFERATIVE DR**
- incipient with microaneurysms and punctate hemorrhages
- moderate—in addition other types of hemorrhages, hard, stringy exudates
- severe (hemorrhages in all 4 quadrants, intraretinal venous changes in 2 quadrants, *beading in one quadrant*).
- **Non-proliferative, early and moderate DR—*background***
  - *microaneurysms*

    located in the inner nuclear layer.
    small red dots
    AFA—early punctate hyperfluorescence

  - *hard exudates*

    located in the external plexiform layer
    small yellowish dots (cherries) (arranged annularly) in posterior pole

  - *retinal edema*

    thickened retina
    FA—late diffuse hyperfluorescence

  - *intraretinal hemorrhages*

    they are punctate or spotted.
    are located at the venous end of the capillaries

  - *hemorrhages in the layer of retinal nerve fibers*

    are given by superficial precapillary arterioles
    flame hemorrhages
    FA hyperfluorescence by masking

- **Preproliferative DR is severe nonproliferative.**
  - *corresponds to ischemic retinopathy*
  - *cotton wool spots*

    small superficial, whitish lesions

FA—focal masking hypofluorescence associated with adjacent capillary non-perfusion

- *intraretinal microvascular anomalies*

  fine vessels between arterioles and venules
  FA—focal hypofluorescence associated with capillary occlusion, without diffusion.

- *venous dilatations, clogging, beading*
- *arterial obliterations, narrowed vessels*
- *hemorrhage*

- **PROLIFERATIVE DR**
  - Mild
  - High-risk
  - Advanced diabetic eye disease

- **Complicated proliferative DR**
  - *intravitreal, retrohyaloid (preretinal) hemorrhages or both; are the most common, can reach the vitreous and cause intra vitreal hemorrhages*
  - *fibrovascular membranes*
  - *hyaloid fibrovascular proliferation*
  - *Tractional RD*
  - *Irian rubeosis - neovascularization*
  - *Macular edema*

Diabetic Maculopathy: DM

- it can be present at any stage
- it is characteristic of type II diabetes in patients with hypertension and dyslipidemia.
- is the most common cause of vision loss in DR [56]
- clinical forms of DM [6, 56]
  - *exudative, edematous maculopathy—EM*

    symptoms: metamorphopsia, central VA decrease
    two clinical forms

    focal exudative maculopathy with—focal foveolar thickening, associated with hard peri foveolar exudates, perimacular microaneurysms, FA late focal hyperfluorescence with good macular perfusion;
    diffuse exudative maculopathy with—diffuse foveolar thickening, FA—late diffuse hyperfluorescence, “flower petal” appearance

  - ischemic maculopathy—IM

relatively normal fovea
FA—shows foveolar capillary non-perfusion
includes two forms

MI with widening of the foveal avascular zone by capillary occlusion
Clinically significant macular edema with

retinal edema located within 500 μm from the center of the fovea
hard exudates within 500 μm from the center of the fovea associated with edema
retinal edema 1500 μm (1 PD) or more from the center of the fovea
FA—capillary nonperfusion;

- mixed forms

- prognostic factors are reserved
  - hard exudates at the macula
  - cystoid macular edema
  - mixed maculopathy
  - severe retinopathy when DR is discovered
- DM treatment
  - local laser photocoagulation laser impacts until the whitish or brown color change of microaneurysms and hard exudates located between 500–3000 μm from the center of the fovea is obtained; spots 50–100 μm/0.10 s
  - grid laser—lower intensity laser impacts are applied in the area of diffuse thickening located more than 500 μm from the center of the fovea and 500 μm from the temporal margin of the papilla;
  - photocoagulation can cause serious complications: subretinal neovascularization (due to dosage error), cystoid macular edema that can aggravate a pre-existing macular edema.
- **DR surveillance** requires annual control of normal fundus or minimal DR and every 4–6 months in moderate DR.
- **Emergencies in DR are:**
  - Severe nonproliferative DR
  - acute maculopathy
  - Proliferative DR complicated with IVH, RD, neovascular glaucoma.
- **Signs of DR progression**:
  - decreased VA, loss of vision, difficult night vision
  - disturbances in the perception of colors
  - blurred vision alternating with normal vision
  - black dots in the field of vision
  - red, mobile spots.

- **Unfavorable prognostic factors**
  - diffuse edema (multiple leakage areas)
  - soft, stringy, numerous exudates (if BP normal)
  - macular ischemia
  - CMO
  - VA below 20/200
  - Incorrectly treated hypertension
- DR treatment
- The therapeutic approach is different depending on the stage of the disease [5, 7, 14, 57].
  - Moderate nonproliferative DR

    medical treatment ±
    laser treatment if there is macular edema
  - Severe nonproliferative RD

    laser treatment
    intravitreal antiVEGF injections for macular edema
    panphotocoagulation if needed
  - proliferative RD

    laser panphotocoagulation instituted immediately after detection of retinal neovascularization
  - Advanced diabetic eye disease

    posterior vitrectomy
- Medical treatment
  - *patient education*
  - *treatment of diabetes with insulin or oral antidiabetics*
  - *medical treatment with*:

    Ginkgo biloba extracts—Tanakan, Bilobil, Optilutein
    flavones—Myrtilene, Difebion, Difrarel
    carotenoids—Lutein, Astaxanthin
    antioxidants—vitamin C, E
    Sermion, Doxilek, Tarosin, Etamsylate
    Mannitol in MO, IVH
    antiglaucomatous drugs
    aldoreductase inhibitors
    beta 1 proteinkinase inhibitors—RUBOXISTAURINE
    minocillin (antibiotic)
    corticosteroids—intravitreal—TRIAMCINOLON, OZURDEX are used in the treatment of diabetic macular edema
    anti-VEGF.

- Intravitreal anti-VEGF injections which are: Pegaptamide (Macugen), Bevacizumab (Avastin), Ranibizumab (Lucentis)
  - produce a decrease in edema and improvement in VA
  - numerically reduce neovessels, limit the size of fibrous membranes after panphotocoagulation (therefore, in large disc neovessels, panphotocoagulation is associated with intravitreal anti-VEGF injections)
  - intravitreal injection risks: endophthalmitis, lens damage, RD, rarely IVH, choroidal H, high IOP, vitreous hernia.
- Laser treatment
  - It is effective for diabetic macular edema, for preventing vision loss (does not restore lost vision).

LASER photocoagulation treatment in DR generates (post-burn) a chorioretinal scar at the level of the RPE with the destruction of the retinal ischemic area and the reduction of the capacity for neovascular proliferation

- **FC laser is directed by FA exploration. The laser can limit the extension of retinal edema, promote its resorption, and through scarring between the RPE and the neuroepithelium limit the serous detachment of the neuroepithelium.**

Laser FC treatment is done transpupillary with green Argon or Krypton red laser (when cataract or vitreous hemorrhage is present), focal laser FC or panretinal FC depending on the stage of DR.

- Photocoagulation treatment can be:
  - **Focal or grid FC** acts on the altered vessels, blocked by the occlusive process, and the laser energy destroys the retinal tissue.
  - **Panphotocoagulation** - PFC - is FC extended over the entire surface of the peripheral retina, except for the region between the vasculature
  - **The major effect of panretinal laser FC is destruction of neovessels and inhibition of VEGF secretion.**
  - **The laser does NOT improve vision directly, but it can prevent its degradation**.
  - **Panretinal FC is indicated in severe NPDR and in all stages of PDR** [51].

    Adverse effects in FCP can be present in the treatment of PRD with various types of laser: vitreous hemorrhages, choroidal detachments, neurotrophic keratopathy, clinically significant macular edema, tractional macular detachment.
    FCP remains the gold standard for the treatment of retinal ischemia and neovascularization in DR, CRVO, retinopathy of prematurity where the laser has proven clinical efficacy

Laser CF treatment in the evolutionary stages of DR

- **Nonproliferative diabetic retinopathy**—severe NDR

- FC panretinal laser can delay the development of DR, proliferative—PDR
- **Proliferative diabetic retinopathy**—affects 2% of type 2 diabetes patients less than 5 years after onset, and 25% of those with diabetes for more than 20 years.
  - PDR is accompanied by abnormal retinal neovessels, microaneurysms, hemorrhages, hard exudates, cotton wool spots
  - The treatment of PDR is:

    intravitreal anti-VEGF (antivascular endothelial growth factor) medication
    intraocular corticosteroid implant—dexamethasone, intravitreal triamcinolone
    Panretinal laser FC with 1000–4000 laser impacts in 3–4 sessions applied to the peripheral retina avoiding risk areas (the procedure is painful)
    vitrectomy if needed

- **Diabetic macular edema DME**
- **Continuous emission laser should NOT be applied for lesions below 300–500 μ from the center of the macula**.
- **DME without central involvement—FC laser is focal continuous or micropulsed**
- **DME with central involvement, controlled diabetes, good VA, focal or grid laser treatment with micropulse laser only if central retinal thickness is less than 350 microns**.
- Treatment of diabetic macular edema:
  - intravitreal antiVEGF injection
  - intraocular dexamethasone implant, intravitreal triamcinolone, for the treatment of clinically significant macular edema and/or persistent macular edema
  - intraocular implant with fluocinolone for chronic macular edema
  - Focal laser FC
  - Grid laser FC in DME, with capillary nonperfusion
  - Vitrectomy as needed, indicated for VA preservation and restoration in persistent vitreous hemorrhage, preretinal membrane, tractional RD, refractory DME.

Pascal multispot noncontinuous wave laser photocoagulation in diabetic retinopathy brings about radical changes in conventional FC parameters, with minimal incidence of side effects during and after laser treatment [51].

- FC laser Pascal, with short duration pulses 0.01 s, in rapid sequences, one after another—pattern, preset by a microprocessor, scan controlled, changed the protocol and increased the therapeutic performance with long-term clinical efficiency.
- Pan FC in the Pascal system (532 nm frequency-doubled YagNd laser) with parameters: spot size 200 μm, pulse duration 20–30 ms, power 300–1000 mv, panFC in 2 sessions, with total number of spots 2500–3000
- For conventional laser—spot 200 μm, pulse duration 100 ms, power 150 mw up to gray-white lesion in 3 treatment sessions with total number of spots 1500.

– **FC laser of the retina with short duration pulses and pattern in DR is much more effective than FCC and much better tolerated by the patient.**

Guided laser photocoagulation—the Navillas system

- Laser photocoagulation with Navillas 577 navigation system is indicated in refractory diabetic macular edema by focal or grid laser coagulation after examination: VA, OCT sd and control, FA, indocyanine green examination.
- After focal treatment, VA improvement, retinal thinning and a significant decrease in macular edema can be observed
- **The advantages of short exposure time in FC multispot discontinuous wave laser in new technologies are:**
- selective treatment, minimal effects on retinal tissue, which limits heat propagation and does not affect the neurosensory retina
- significant patient comfort with minimal perceived pain
- reduces to the complete avoidance of side effects at the cellular level
- combines high-performance imaging with treatment
- **Post-treatment FC laser: VA remains stable in 70%, improves in 15% or may degrade, reserved prognostic factors being: hard macular exudates, CME mixed maculopathy (edematous and ischemic), severe DR** [25].
- FC can lead to complications such as cystoid macular edema (CME) by aggravating a pre-existing macular edema, it can be associated with serous detachment of the neuroepithelium, subretinal neovascularization (possible dosing error in intense FC in a patient with extensive DR), vitreous hemorrhage, posterior detachment vitreous.
- **Treatment of nonproliferative DR** is directed at clinically significant macular edema

  – laser treatment at the level of the microaneurysm—spots 100 μm/0.10 s, enough to produce color changes (whitening, blackening)
  – horseshoe grid laser, protecting the interpapillomacular space [55].

- **The treatment of proliferative DR** is PFC laser panphotocoagulation—which reduces the risk of vision loss

  – laser treatment indications—PFC

    NVD or NV within 1 PD of optic disc
    NVD >1/2 PD associated with IVH or preretinal

  – laser treatment can be started even earlier if it is

    difficult collaboration
    kidney damage, pregnancy
    cataract

  – TECHNICAL

    it begins outside the arches at 1–2 PD inferior temporal from the center to the periphery
    spot 200–300 μm, increasing towards ora serrata; the distance between spots equal to their size; moderate intensity with a white scar

600–800 spots per session (→1300)
Between sessions 3–4 weeks
if CME, they are treated 4–6 weeks before PFC.

- **Posterior vitrectomy**—is indicated in complications
  - Persistent, severe intravitreal hemorrhage
  - Tractional RD with macular involvement
  - Secondary RRD
  - dense and persistent premacular retrohyaloid hemorrhage
  - fibrovascular proliferation at the level of the papilla with vitreoretinal tractions
  - macular edema secondary to vitreoretinal thickening and/or traction
  - the progression of an iris rubeosis
  - cataract
  - neovascular, phantom cell glaucoma.

Retinopathy of Prematurity (ROP)

- ROP is a vasoproliferative retinopathy that occurs in premature infants with a gestational age of less than 32 weeks, with a low weight of less than 1500 g, exposed to oxygen therapy [24].
- The normal retinal vascularization with a radial disposition around the ON involving the temporal periphery of the retina is definitive after 15 days after birth.
- Lesions in ROP are located in three concentric areas around the papilla
  - zone 1 corresponds to a circle with a radius equal to twice the interpapillomacular distance
  - zone 2—concentric with zone 1—has the nasal border at the ora serrata and the temporal border at the equator.
  - zone 3 is the crescent-shaped temporal surplus zone (this zone is the last to be vascularized in the premature eye); this time zone is the earliest location of ROP.
  - **Risk factors**
  - premature birth—less than 32 weeks of gestation
  - low birth weight—below 750 g 90% risk, between 1000–1250 g 45% risk ROP
- Classification of ROP [14]
  - *Stage 1*
- white line of demarcation between the avascular retina (white) located anteriorly in the periphery of the fundus and the vascularized area.
- vascular arches perpendicular to the line of demarcation (“broom” arrangement);
  - *Stage 2*

- pinkish white sponge between the vascular and avascular area with intraretinal neovascularization with arterial and venous tortuosity;
- evolution towards regression (constant) or towards stage 3;

  – *Stage 3*

- extraretinal neovascularization with extensive fibrovascular proliferation in zone II and in the vitreous, perpendicular to the plane of the retina, which can give: stage 3a (discreet), 3b (moderate), 3c (severe);
- stage 3 plus with dilated vessels near the the optic disc (can coexist with stage 2, 3 requires laser treatment);
- the "plus" form shows associated signs:

  the pupil hardly dilates
  the iris vessels are congested
  venous and arteriolar dilatations in the posterior pole
  VH and important preretinal

  – *Stage 4*

- Tractional RD without macular damage (starts from stage 2 sponge);

  – *Stage 5*

- Total RD, tunneled through proliferative tissue with substages 5a—open tunnel, 5b—closed tunnel;
- The evolution of ROP

  – stages 1 → 3, rarely 4 may regress rapidly or slowly (total resolution in stages 1, 2); the first sign of regression is the cessation of neovascular proliferation with the diminution of the sheen of the burlet;
  – total evolution towards 1 year, then slow evolution with stationary and aggravating phases, asymmetric, on both eyes.

- **Complications**

  – stage 1, 2: myopia, anisometropia, strabismus, amblyopia, macular ectopia, RD;
  – stage 3, 5: nystagmus, glaucoma, cataract, iris rubeosis, VH, RD, band keratopathy, phthisis bulbi.

- **Prophylaxis**

  – competent supervision and examination of premature infants under 1500 g and under 32 weeks
  – detection of other determinations of the premature
  – monitoring of oxygenation
  – **early detection of RP stage**
  – **periodic ophthalmological follow-up**

- **Curative treatment**

- **Laser and cryotherapy** in the avascular area improves the prognosis visibly, the laser being more effective and less invasive [51].

  confluent photocoagulation with diode or argon laser on the entire peripheral avascular area

- Sequelae of ROP post-FC laser: macular ectopy, myopia, strabismus, angle-closure glaucoma, cataract, vitreous hemorrhages, sickle macular fold.
- **Vitrectomy with or without lensectomy** in stages 4, 5 and stage 3 with evolutionary potential

  associated lensectomy in stage 5
  vitrectomy for tractional RD gives questionable results.

Coats Disease

- Non-hereditary exudative proliferative retinal vascular disease, with vascular abnormalities with telangiectasias, retinal aneurysms, intra-, subretinal exudates and RD, without signs of inflammation [58].
- More common in men, unilateral, progressive 50% with detection in the first decade through complications: VA decrease, leukocoria, strabismus, complicated cataract, neovascular glaucoma [59, 60].
- Coats disease may be associated (rarely) with: Alport syndrome, fasciculo-scapulo-humeral dystrophy, muscular dystrophy, tuberous sclerosis, Turner syndrome
- The typical form in Coats disease begins in the first decade (on average at 5 years) with **leukocoria,** decreased vision, strabismus, complicated cataracts, neovascular glaucoma.
- The spectrum of the disease is variable, in elderly adult patients
- Classification:
  - Stage 1—only telangiectasias
  - Stage 2—extrafoveal (2a) or subfoveal (2b) exudation
  - Stage 3—subtotal (3a) or total (3b) exudative retinal detachment
  - Stage 4—total retinal detachment, neovascular glaucoma
  - Stage 5 (advanced)—extensive, serious complications
- Clinical signs
  - ocular:

    asymptomatic (if the lesions are peripheral);
    vascular alterations: small vessels with telangiectasias, frequent temporal arterial aneurysmal dilatations in the periphery of the retina;
    exudative manifestations in the periphery of the retina, which can extend to the macula, possibly complicating with exudative RD, VH, cataract, rubeosis iridis, neovascular glaucoma;

  - general:

scapulo-humeral muscular dystrophy, Turner syndrome, cerebral vascular malformations, mandibulo-facial dysostosis.

- Evolution without treatment, unfavorable with treatment, prognostic improvement
- Complications: cataract, leukocoria, rubeosis iridis, secondary glaucoma, total retinal detachment, uveitis, globe phthisis
- Treatment [61]:
  - clinical follow-up of moderate forms;
  - early treatment of vascular anomalies by laser photocoagulation of telangiectatic areas without RD; allows resorption to be achieved and can stop the unfavorable evolution of the disease; caution with laser FC of macular ectasias
  - FC argon laser or frequency-doubled Yag-Nd under AFG control in the absence of RD directly on dilatations and aneurysms
  - cryotherapy in case of RD and peripheral retinal vascular anomalies, when photocoagulation is not effective;
  - vitreoretinal surgery in RD

Miliary-Leber Aneurysm

- Onset 30–50 years with telangiectasias located in the temporal periphery and hard exudates, which can sometimes reach the macula.
- The prognosis is related to the involvement of the macula by hard exudates.
- Treatment—LASER photocoagulation.

Eales Disease

- Eales disease is an obliterative, idiopathic, bilateral asymmetric retinal vasculopathy affecting the peripheral retina in the young adult (often of Indian or Middle Eastern origin), aged 20–30 years, preferably male
  - It is characterized by retinal venous anomalies, with retinal periphlebitis and recurrent vitreous haemorrhages, the disease being a primary, non-inflammatory idiopathic retinal perivasculitis of the walls of the peripheral vessels of the retina [62]
  - The evolution is towards vascular occlusion, peripheral neovascularization, spontaneous, unilateral vitreous hemorrhage
- At the onset, the disease may be asymptomatic or the patient perceives progressive or sudden blurring of vision, sometimes a significant, painless decrease in visual acuity

- Eales disease has unknown etiology and multifactorial character including: autoimmune diseases, oxidative stress, *Mycobacterium tuberculosis*, coagulation disorders
- The clinical evolution is staged [5, 57]:
  - The inflammatory stage with:

    Decreased visual acuity
    Mobile flakes
    Perivascular clots
    Mobile cells *in the vitreous*
    microaneurysms
    Intraretinal hemorrhages with white, sclerotic phantom vessels
    Signs of anterior chamber inflammation with keratic precipitates and positive Tyndall
    Cystoid macular edema

  - Ischemic stage due to peripheral retinal nonperfusion with retinal vein sclerosis, with macular or choroidal involvement
  - Fibroproliferative stage with:

    neovascularisation
    Retinal hemorrhages
    Tractional retinal detachment

- Differential diagnosis is made with other causes of neovascularization:
  - Central retinal vein occlusion
  - Diabetic retinopathy
  - Sickle cell retinopathy
  - Sarcoidosis
  - Tuberculosis
  - Systemic lupus erythematosus
  - Other collagen diseases
  - Multiple sclerosis
- The positive diagnosis of Eales disease is made by exclusion, excluding other inflammatory or neovascularization causes
- The evolution is variable:
  - Spontaneously regressive (rare)
  - Toward the severe fibroproliferative phase with complications: neovascularization, retinal detachment, recurrent vitreous hemorrhage
  - Sequelae with secondary blindness and other chronic complications
- Complications:
  - Recurrent vitreous hemorrhage
  - Tractional retinal detachment
  - Neovascular glaucoma

  - Rubeosis iridis
  - Cataract

- Treatment:
  - In the initial perivascularitis stage:

    Periocular corticotherapy
    Oral or intravenous systemic corticosteroid therapy
    Immunosuppressants: Azathioprine, Ciclosporin
    Sometimes antituberculosis treatment remains debatable

  - In the ischemic and proliferative stage:

    Laser photocoagulation of the nonperfused retina when neovascularization develops
    Laser FC in the proliferative ischemic retinal phase can stabilize the lesion, improve the disease anatomically and functionally during a transient period.
    If there is vitreous hemorrhage that prevents examination of the fundus, peripheral cryotherapy is practiced which can be applied for avascular peripheral retinal ablation
    Vitreoretinal surgery if the vitreous hemorrhage persists for more than 3 months

Primitive Macular Telangiectasia (Ideopathic/Juxtafoveal/ Perifoveal)

- Represents a group of vascular disorders affecting perifoveal capillaries confined to the juxtafoveal region 1–199 μm from the center of the fovea
- **Type 1A—Congenital unilateral parafoveal telangiectasia**
  - Onset in men aged 40–50 years
  - fundus exam shows temporal telangiectasia of the fovea, with a diameter of 1–2PD, bordered by hard yellowish exudates
  - Decreased visual acuity to 20/40 due to macular edema and exudates
  - It could be the average adult form of Coats disease
  - FA shows capillary dilatation, late diffusion, and macular edema with petaloid effusion
  - During the OCT examination, hyporeflective cavities appear, possibly atrophic areas
  - The treatment is by focal laser photocoagulation of the diffusion areas
- **Type 1B—Unilateral idiopathic parafoveal telangiectasia**
  - Onset at 40–50 years

- Clinical signs—telangiectasia limited to an hour sector at the edge of the central avascular zone
- FA—focal capillary dilatation without diffusion
- OCT
- Good prognosis
- It does not require treatment

- **Type 2—Acquired bilateral idiopathic telangiectasia**
  - Onset at 50–60 years
  - Equal distribution in both sexes
  - It is bilateral and asymmetrical
  - Clinical signs:

    Telangiectasia witheen 1PD, temporal to the fovea or surrounding the fovea
    Stellate plaques of hyperplasia of the pigment epithelium
    Multiple juxtafoveolar refractive white dots and small solitary yellowish central deposits

  - FA—capillary dilatations outside the avascular zone and late diffusion
  - OCT
  - choroidal neovascularization
  - Treatment:

    It is indicated when choroidal neovascularization develops and then requires laser photocoagulation
    Intravitreal anti-VEGF for subfoveal neovascularization—Bevacizumab (Avastin) 1.25 mg—does not prevent decrease in visual acuity

- **Bilateral perifoveal telangiectasia with capillary obliteration**
  - Rare form, presenting at 50–60 years old, without sex predilection, with progressive loss of vision due to marked aneurysmal dilatation and telangiectatic perifoveal capillary obliteration
  - Fundus examination reveals severe telangiectasia, perifoveolar capillary occlusions, and optic atrophy
  - FA:

    Aneurysmal dilatation of the capillary bed
    Progressively extensive macular area of capillary nonperfusion
    Choroidal neovascularization

  - Treatment is recommended when choroidal neovascularization develops:

    Focal laser photocoagulation
    Intravitreal anti-VEGF agents—1.25 mg Bevacizumab (Avastin)

- A neurological consultation is recommended

Familial Exudative Vitreoretinopathy: Norrie Disease—XLR

- Rare eye disease due to a vascular development defect of the peripheral retina, has a slowly progressive, bilateral evolution, similar to retinopathy of prematurity, but with a child born at term, without exposure to oxygen
  - Ocular findings are asymmetric and are associated with systemic manifestations
- The evolution is stadial:
  - *Stage 1*:

    The lesion begins in the temporal peripheral retinal area with peripheral cystoid degeneration, microaneurysms, telangiectasias, vascular engorgement
    Asymptomatic in 73% of cases, but strabismus and nystagmus may be present
  - *Stage 2*:

    Peripheral vessels dilated, tortuous
    Fibrovascular neovascularization
    Sub/intraretinal exudation
    Macular and papilla traction with macular ectopy
    Sickle retinal fold
    Localized retinal detachment
    Decreased vision
  - *Stage 3*:

    Rhegmatogenous retinal detachment
    Retinal folds
    Massive subretinal exudation
    Band keratopathy
    Complicated cataract
    Neovascular glaucoma
    leucocoria
    Myopia
    Amblyopia, strabismus
    Retinal detachment difficult to treat due to vitreoretinal proliferation
- Systemic is associated with deafness and mental retardation
- Treatment:
  - Prophylactic—laser photocoagulation in avascular retina—is controversial

- Vitrectomy for retinal detachment.

Irradiation Retinopathy

- Radiation retinopathy is the vasculopathy that occurs after the treatment of intraocular tumors, sinus, orbital or nasopharyngeal tumors, by brachytherapy or external radiotherapy
- After a total radiation dose of 3000–3500 rad, at an interval of 6 months—3 years after radiotherapy, radical retinopathy may occur
- It is often asymptomatic at the onset, vision loss gradually sets in after the involvement of the macula
- The dundus examination finds:
  - Microaneurysms, telangiectasias
  - Cotton wool spots and hard exudates
  - Retinal hemorrhages
  - Macular edema, disc edema
  - Vascular blockages
  - Disc, retinal, iris neovascularization
- Treatment:
  - Grid laser photocoagulation of macular edema (spot 50–100 μm) and proliferative retinopathy
  - Systemic corticosteroid therapy for papillopathy
  - Intravitreal—Triamcinolone 4 mg (Kenalog) and antiVEGF—Bevacizumab 1.25 mg—decreases macular edema and improves vision
  - Panretinal photocoagulation with 1200–1600 applications (spot 500 μm) if choroidal neovascularization complicates the course

Incontinentia Pigmenti

- X-linked AD condition, fatal in boys, present in females
- Eye features:
  - Microphthalmia
  - Cataract
  - Squint
  - Retinal neovascularization

  - Vitreous hemorrhage
  - Tractional retinal detachment
  - Optic atrophy
- Systemically associated with anomalies:
  - CNS
  - dental
  - skin
- Treatment:
  - Laser photocoagulation for the area of the ischemic retina where neovascularization develops
  - Vitrectomy in vitreous hemorrhage and retinal detachment.

Retinopathy in Blood Diseases

Anemia
- Retinopathy is rare and very rarely of diagnostic importance
- Clinical signs at fundus examination [41]:
  - Superficial flaming intraretinal hemorrhages, sometimes having a white center—Roth spots
  - Roth spots are found in pernicious anemia and aplastic anemia
  - Cottony nodules
  - Very rarely—exudates
  - Retinal edema
  - Venous changes
  - Vitreous hemorrhage in patients with hemoglobin below 8 g/100 mL
- Retinopathy is often more severe if thrombocytopenia is associated
- Optic neuropathy may be present in pernicious anemia
- Iinternal medicine and hematology control and treatement is recommended
- Retinopathy is resolved by treating the anemia

Leukemia
- Ocular involvement in leukemia can reach up to 50% of cases, with patients generally being asymptomatic
- Retinopathy is rare and is caused by the association of anemia, thrombocytopenia and hyperviscosity
- Clinical signs on fundus examination:
  - Superficial flame intraretinal, preretinal, and vitreous hemorrhages
  - microaneurysms
  - Roth spots
  - Cotton wool spots

  - Dilated, tortuous vessels
  - Perivascular exudates
  - Papillary edema
  - Rarely, choroidal infiltrates (3%) with choroidal thinning and serous retinal detachment

    The fundus can take on a "leopard skin" appearance due to choroidal infiltration
    Neovascularization can develop over time in chronic myeloid leukemia

- In addition to retinopathy, other manifestations are possible in leukemia:
  - Orbital involvement, especially in children
  - Pseudohypopion
  - Spontaneous subconjunctival hemorrhages
  - Hyphema
  - Optic nerve infiltration
- The treatment is hematological, oncological, internal medicine

Hyperviscosity
- Hyperviscosity retinopathy is accompanied by:
- Venous dilatations with vascular tortuosity
- Retinal hemorrhages
- Sometimes venous occlusions

Sickle Cell Retinopathy
- "Sickle" hemoglobinopathies produce non-proliferative and proliferative vascular changes, resulting from hemoglobin mutations, with alteration of hemoglobin conformation and deformation of erythrocytes.

Phacomatosis

- They are hereditary conditions, AD with incomplete transmission (apart from Sturge–Weber and Wyburg–Mason syndrome which are not hereditary and ataxia telangiectasia with AR transmission) [5].
- They are characterized by the simultaneous damage to the eye, skin and CNS by phacomas.
- The phacomatoses are:
  - Von Hippel Lindau retinal angiomatosis
  - Neurofibromatosis type 1—Von Recklinghausen disease
  - Neurofibromatosis type 2
  - Bourneville tuberous sclerosis

  - Encephalotrigeminal angiomatosis—Sturge Weber Krabbe syndrome
  - Louis Barr ataxia-telangiectasia syndrome
  - Racemic hemangioma—Wyburn-Mason syndrome

- Phacomatoses are congenital neurocutaneous syndromes characterized by the presence of hamartomas located ocularly and systemically in the skin and CNS
  - Most have AD transmission with incomplete penetrance, except Sturge Weber and Wyburn-Mason syndromes which are not hereditary and ataxia-telangiectasia which is AR
- Genetics of phacomatoses (Friedman) [29]
  - Neurofibromatosis type 1—without pheochromocytoma—chromosome 17
  - Neurofibromatosis type 2—with pheochromocytoma—chromosome 22

    2A—low risk renal carcinoma
    2B—high risk renal carcinoma
    2C—isolated pheochromocytoma

  - Von Hippel Lindau disease—chromosome 3
  - Bourneville tuberous sclerosis—chromosome 11
  - Sturge Weber syndrome—non-hereditary
  - Wyburn-Mason syndrome—non-hereditary

Von Hippel Lindau Retinal Angiomatosis (Retinal Capillary Hemangioma)

- Chromosome 3p26–p25 with incomplete penetrance
- 50% bilateral
- Hamartoma located in:
  - Eye—hemangioblastoma (45%)
  - Brain—cerebellum
  - Kidney—adrenal
- Ocular—angioma/hemangioma or retinal hemangioblastoma [31]:
  - Frequently located supero-temporally
  - Round mass located in the middle periphery of the retina, red, bilateral, single or multiple, with dilated retinal artery and vein
  - Lipid exudates in the macula or around the macula and papilla
  - Exudative retinal detachment
  - Vitreous hemorrhage
  - Epiretinal membrane
  - Macular edema

- Systemic—retinal hemangiomas can be associated with:
  - CNS tumors 25%—cerebellar hemangioblastoma (60%), pons, spinal cord (rare)
  - Visceral lesions—renal cyst or tumor, pancreas, liver, adrenal gland, lung (include renal carcinoma 25%, pheochromocytoma 5%)
  - Hemangioma of the face
  - Paroxysmal hypertension
  - Ataxia
- Required investigations: EOG, CT, MRI (Gadolinium)

von Hippel's Disease

- Retinal angiomatosis, diagnosed at an average age of 25, uni-bilateral, asymptomatic or VA decrease.
- Clinical signs
  - Retinal angioma (round, pink, bright mass 1/2–1 PD) peripherally located, juxtapapillary without abnormal vessels (very rare) or with two dilated and tortuous vessels (artery and vein) that grow over time and may accompany RD localized, total exudative and neovascular glaucoma.
- Variable evolution with spontaneous involution, recurrence after treatment.
- Treatment—clinical follow-up, laser photocoagulation, cryotherapy, vitrectomy for RD ± VH.

Von Hippel-Lindau Disease

- It associates vascular retinal lesions with general signs:
  - CNS hemangioblastoma
  - cyst in kidney, pancreas, epididymis, ovary
  - renal carcinoma
  - pheochromocytoma
  - neurological manifestations through cerebellar, bulbar, medullary hemangioma
- Treatment
  - photocoagulation, cryotherapy, vitrectomy
- Treatment:
  - Small lesions (<500 μm) without exudates and subretinal fluid should be followed up clinically

- Small lesions can benefit from argon laser photocoagulation, spots can be applied directly to the lesion if it is less than 2.5PD in diameter
- Larger tumors (more than 3 mm in diameter), those previously located or when the media are not transparent can benefit from cryotherapy
- Large tumors, if needed, benefit from laser therapy combined with cryopexy or diathermy
- In the case of tumors over 4.5 mm or tumors resistant to photocoagulation or cryotherapy, external radiotherapy is an option
- Potential treatment with anti-VEGF
- In severe forms—surgical excision with risk of recurrence and complications

Neurofibromatosis Type I: Von Recklinghausen

- It is characterized by multiple tumors in the skin, CNS and other organs, associated with specific skin manifestations in the form of "coffee with milk" spots and neurofibromas [37, 63].
- AD (and sporadic cases) affecting chromosome 17q11.
- Ocular
  - frequent, variable changes
  - eyelid plexiform neurofibroma at 2–5 years (it is the first skin sign in NF I) that can invade the orbit
  - neurofibromas in the eyelid, orbit
  - **ON glioma (most common manifestation)**
  - ON sheath meningioma
  - congenital glaucoma
  - possible: Lisch nodules, retinal astrocytoma, choroidal hamartoma
- General
  - skin lesions

    "coffee with milk" spots
    plexiform neuroma, neurofibromas, melanodermic nodules, nevi, achromic spots
    peripheral nerve lesions with plexiform neuroma (possible malignant CNS degeneration)
    CNS lesions with neurinoma, schwannoma, meningioma, arachnoid cysts, meningocele, glioma NO
  - visceral injuries

    sympathetic, parasympathetic chain tumors
    megacolon, mega ureter
    pheochromocytoma

  - skeletal injuries

    short stature, macrocephaly, facial hemiatrophy, bone dysplasia

- Positive diagnosis of NF I—two elements of the following:
  - five or more "coffee with milk" spots
  - 2 or more neurofibromas, 1 plexiform neuroma
  - 2 or more Lisch nodules
  - ON glioma
  - Moles
  - bone lesions: dysplasia of the sphenoid, thinning of the bones of the cortex
  - first degree relatives with NF

Neurofibromatosis Type II

- Rare, mutation on chromosome 22, onset 20–30 years [24]
- **Characterized by bilateral acoustic neuroma associated** (or not) with brain tumors
- Ocular
  - retinal, choroidal tumors
  - posterior subcapsular cataract
  - combined hamartoma of RPE and retina
  - ON sheath meningioma
  - ON glioma (rare)
- General
  - deafness
  - tinnitus
  - balance disorders
  - look "donkey skin", spots "coffee with milk"
  - cardiac, renal rhabdomyoma, angiomyolipoma
  - early mortality

Bourneville's Tubeous Sclerosis

- Rare condition, AD, chromosome 9q34, 16p31, sporadic with clinical manifestation in childhood, clinically manifested by the triad: sebaceous adenoma, mental retardation and epilepsy associated with hamartoma in the brain, retina, viscera.
- Ocular
  - astrocytic hamartoma in the retina and/or ON

small gelatinous gray plaques, 1–2 DP, superficial, poorly demarcated, anterior to vessels, located at posterior pole
large nodular tumors with a muriform, cystic appearance in the region of the optic disc
retinal, iris depigmented areas
palpebral, subconjunctival nodules

Sistema

- CNS—intracerebral astrocytoma manifesting as seizures in *new born*, mental retardation, Jacksonian epilepsy, mental deficiency
- viscerally
  - lung, bone injuries
  - renal angiomyolipoma
  - cardiac rhabdomyoma
- cutaneous
  - sebaceous adenoma of the cheeks with vascularized red papules with a "butterfly" distribution
  - depigmented spots "achromic nevi"
  - painful, cutaneous fibroids under nails.

Encephalo-Facial Angiomatosis: Sturge–Weber–Krabbe Syndrome

- It is an encephalotrigeminal angiomatosis (nevus flammens) associated with choroidal hemangioma, leptomeningeal angioma and homolateral congenital glaucoma, ± epilepsy [34].
- Non-hereditary, no sex predisposition.
- Ocular
  - on the side of the hemangioma
  - **palpebral, scleral hemangioma** with dilated conjunctival vessels
  - **diffuse choroidal hemangioma**
  - retinal arterio-venous malformations
  - homolateral iris heterochromia
  - **congenital glaucoma, juvenile** in 30% with severe evolution, produced by angle abnormalities.
- Sistemic
  - cutaneous angioma located on the face, located on the first, second branch of the V th nerve
  - appearance nevus flammens, which does not expand with age, but intensifies in coloration
  - homolateral hemiface hypertrophy

  - neurological signs with: seizures, variable mental retardation, diffuse meningeal angiomas.

Louis Bar Syndrome: Ataxia/Telangiectasia

- It associates cerebellar ataxia with bilateral oculocutaneous telangiectasia
- Ocular
  - conjunctival vessels with telangiectasias
  - squint
  - nystagmus
- Sistemic
  - slowly progressive limb ataxia in the first 10 years
  - extrapyramidal disorders
  - mental retardation
  - diabetes
  - often neoplasms

Racemos Hemangiom: Wyburn/Mason Syndrome

- Rare unilateral, non-hereditary condition, with arteriovenous malformations located at the level of the retina, thalamus, brain, with facial nerves and sometimes mental retardation
- Ocular:
  - Racemic hemangioma of the retina (arterio-venous malformation with tortuosity and vascular shunts that may extend to the optic tract, chiasm ± optic atrophy)
  - It can be complicated with intraocular hemorrhage or glaucoma
- Systemic:
  - Arterio-venous malformation of the face, orbit, brain (racemus hemangioma) that can generate neurological disorders directly by compression or by infarction, with: epilepsy, paresis, nerve palsies, seizures, hydrocephalus, mental disorders
  - Racemic hemangioma in the brain is congenital but non-progressive
- Racemose hemangioma of the retina may be present concurrently with racemose hemangioma in the ipsilateral midbrain.

Metabolic Diseases of the Retina

- They include a group of hereditary diseases, in which the metabolism of some cellular components is deficient due to the lack of some lysosomal enzymes; over time, abnormal metabolic products (glycoproteins, phospholipids) accumulate in intraocular tissues (and retina) disrupting their functioning (or even cell death) [10].
- ***SPHINGOLIPIDOSES***—are defects in glycolipid metabolism, with enzyme deficiency and accumulation of sphingozymes in vascular and nervous tissues.

Tay-Sachs disease—gangliosidosis type 1 (familial infantile amaurotic idiocy)
- AR present in the first year of life, through the accumulation of lipids in the retina, brain
- ocular
  - cherry red macula
  - optic atrophy
- Sistemic
  - mental retardation
  - progressive neurological determinations

Sandhoff disease—Tay-Sachs-like gangliosidosis type II.
- Generalized gangliosidosis
- eye—cherry red macula
- general
- skeletal abnormalities at birth
- edema of the face and extremities.
- Niemann-Pick disease
  - Sphingomyelin-deficient AR
  - ocular

    cherry red macula
    optic atrophy
    corneal opacities
  - general—varied clinical manifestations—no mental retardation.
- Gaucher disease
  - AR, glucocerebroside deficient
  - ocular

    cherry red macula
    white spots on the retina
- Fabry disease
  - Sex-linked AR, alpha-galactosidase-deficient AD
  - ocular

cornea verticillata
posterior crystalline opacities
aneurysmal conjunctival dilatations
retinal vascular tortuosity
it is not cherry red macula

– general

cutaneous telangiectasias
paresthesia
hypertension
vascular thrombosis
renal insufficiency
anemia

Mucolipidoses

- disturbances in glycoprotein metabolism
- ocular
  - cherry red macula
  - retinal pigment mobilizations
- general
  - facial dysmorphism
  - skeletal abnormalities
  - psychomotor retardation

Mucopolysaccharidoses

- lysosomal enzyme deficiency with accumulation of mucopolysaccharide acid.
- AR except sex-related type II.
- ocular
  - decrease in VA
  - retinal pigment mobilizations, which can simulate pigmentary retinopathy
- general
  - mental retardation
  - skeletal anomalies, reduced joint mobility
  - hepatosplenomegaly
- Clinical forms of MPZ
  - Hurler syndrome—IH (1a)
  - Scheie syndrome—IS (1b) both with corneal retardation and retinopathy
  - Hunter syndrome—II
  - Sanfilippo syndrome—III both only with retinopathy

- syndrome IV
- Marquito-V syndrome
- Maroteaux-Lamy syndrome—VI both only with corneal changes
- Sly syndrome—VIII—no corneal changes, no retinopathy.

Cystinosis

- AR, by accumulation of cystine crystals in tissues (conjunctiva, cornea, uvea, lens, retina in RPE)
- child—nephrotic form
- ocular
  - high photophobia
  - deposits in the conjunctiva and cornea
  - "salt, pepper" fundus
- general
  - Fanconi syndrome
  - growth disorders
  - polyuria
  - renal insufficiency
  - death before puberty
- adolescent: medium nephropathy, visual disturbances
- adult: benign, without kidney problems.

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Chapter 14
Ophthalmological Pathology and Management in Eye Disease: Infectious and Inflammatory Disease of the Vitreous, Retina and Choroid

Marieta Dumitrache

Abstract **Accute retinitis** is retinal metastatic infections in edophtalmitis, panophtalmitis; **subaccute retinitis**—presents in bacterial retinochoroiditis and they are specific retinitis: **bacterial** (sifilis, TBC, Lyme), **fungi**, **parasites**. **Viral** disease of the retina are accute retinal necrosis ARN, progressive herpetic retinal necrosis PORN, CMV retinitis, HIV infection. **Parasitic** retinal infections are: toxoplasmosis, toxochariasis **inflammatory disease**: Vogt-Coyanagi-Harrada sarcoidosis sympathetic ophtalmithes MEWDS, serpiginous choroiditis.

Keywords Retinitis · Retinochoroiditis · Neuroretinitis · ARN PORN · Toxoplasmosis · Lyme · TBC · Inflammatory diseases

Infectious inflammatory diseases of the retina can be:

- retinitis—inflammatory process located in the retina
- chorioretinitis—inflammation of the retina and choroid
- neuroretinitis—inflammation of the optic disc and the peripapillary retina
- retinal vasculitis—inflammation of the retinal vessels.

Retinitis

- Nonspecific retinitis with acute, subacute manifestation [1]
  - *Acute retinitis*

    Is a retinal metastatic infection in endophthalmitis, panophthalmia

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- Subacute Roth retinitis

  is present in patients with subacute bacterial retinochoroiditis and is characterized by hemorrhages in the posterior pole of the retina, which have a white dot in the center—Roth spots
  is present blurred vision if the macula or papilla is involved

- Specific considerations can be [2]:
  - bacterial—syphilis, TB, leprosy, Lyme, Whipple, brucellosis
  - viral—ARN, PRN, CMV, HIV, rubella
  - fungal
  - parasitic

Bacterial Retinochoroiditis

Acquired and Congenital Syphilis

Syphilis is the sexually transmitted infection by treponema pallidum in which the ocular determinations are multiple:

- Retinochoroiditis is present in the secondary stage and may be associated with syphilitic meningitis
- Bilateral retinitis associated with retinal vasculitis and panuveitis
- Progressive retinal necrosis in AIDS patients
- Pseudoretinitis pigmentosa with progressive loss of vision and nyctalopia
- Syphilitic neuroretinitis manifests with papillitis with flaming hemorrhages, vascular occlusions, stellate macular exudates that may evolve with decreased vision through optic atrophy [3]

Other eye conditions: anterior uveitis, interstitial keratitis, neuroretinitis, Argyll Robertson pupil, conjunctival chancre, oculomotor palsies

Treatment [4]
- Penicillin G12-24 MU iv/day—10–15 days
- Extensilin 2.4 MU/day 10–15 days im
- Oral amoxicillin 3 g × 2/day for 28 days
- Oral tetracycline or erythromycin 500 mg × 4/day, 30 days in penicillin allergy

Tuberculosis

TB can affect the uveal tract partially or completely [5]
TBC lesions on fundus are:

- focal, multifocal choroiditis
- extensive disseminated choroiditis with development of granulomatous tissue

- TB choroiditis with chronic evolution associated with MENINGITIS, present in children, in late stages

Other ocular manifestations in TB: granulomatous anterior uveitis, periphlebitis, panuveitis, choroidoretinal granuloma very rarely unique, can be confused with retinoblastoma, pseudoglioma [1]

Treatment—combination of antituberculosis antibiotics (minimum 3): rifampicin, isoniazid, pyrazinamide or ethambutol for 12 months.

Lyme Disease

- It is the ocular and systemic infection with the spirochete Borelia burgdorferi.
- Neuro-ophthalmological manifestations of spirochete infection are:
  - Neuroretinitis
  - Oculomotor palsy
  - Pigmentary retinopathy
  - Multiple cranial nerves palsies
  - Optic atrophy
  - Papillary edema
  - Bilateral mydriasis

Other ocular manifestations: intermediate uveitis, interstitial keratitis, conjunctivitis, episcleritis, orbital myositis, retinal vasculitis, vitritis, VIIth palsy or paresis (in endemic areas 25% of Bell's palsies are in Lyme disease)

Treatment [6]
- Oral doxycillin 100 mg × 2/day—3 weeks
- Amoxicillin, both given in early stages
- in complicated forms Penicillin or Ceftriaxone iv

Whipple's Disease

It is a large intestine disease responsible for malabsorption associated with arthropathy, skin hyperpigmentation, cardiopulmonary and CNS damage, weight loss, fatigue, abdominal discomfort, diarrhea.

- etiologically, it is caused by a gram-positive germ—*Actinomyces* called Tropherma Whippeli with a predisposition to immunodeficiencies

Ocular
- intermediate uveitis
- retinal periphlebitis

Treatment

- Streptomycin and Benzylpenicillin minimum 2 weeks followed by Sulfamethoxazole 800 mg and Trimethorin 160 mg orally × 2/day for 1 year

Brucellosis

- It's the infection with Brucella abortus from cows through ingestion of unpasteurized milk or B. melitensis from goats [7]
  - acute phase: fever and systemic disease with liver, splenic involvement, leukopenia and lymphocytosis
  - subacute phase: intermittent fever and ocular manifestations with:

    decreased vision
    chorioretinitis with typical retinal lesions, with clear edges with perilesional hemorrhages
    chronic granulomatous uveitis
    secondary glaucoma
    occasionally papillitis

  - treatment
  - doxycillin 100 mg × 2/day and
  - streptomycin 1 g/day im
  - late-onset retinochoroiditis requires treatment with:

    ofloxacin 800 mg/day orally and
    rifampicin 900 mg/day orally for 6 weeks with periodic control of fundus

Viral Diseases of the Retina

Acute Retinal Necrosis (ARN)

- It is unilateral/bilateral vaso-occlusive necrotizing retinitis, caused by infection with herpes viruses: VZV, SDV, HSV2, CMV, chickenpox
  - it affects patients between 20–60 years old, immunocompetent, but also patients with different degrees of immunosuppression
  - dermatological systemic viral manifestations may coexist
  - most cases of ARN are due to secondary reactivation of a herpes infection [8]

Clinical

- well-demarcated areas of peripheral retinal necrosis with rapid progression of circumferential necrosis, 7–10 days
- occlusive vasculitis
- moderate vitreous inflammation

Complications: uveitis, RD, blindness

Treatment

- intravenous, intravitreal, oral antivirals:
- Acyclovir—iv 5–10 days followed by oral acyclovir 400–600 mg/day for 5 days—6 weeks, may control progression of acute retinitis
- Famciclovir—500 mg orally × 3/day—3 months—or intravitreal
- Valaciclovir—1 g × 2/day—3 weeks—intravitreal or oral
- Valganciclovir—900 mg × 2/day
- anticoagulants to prevent obstructive vascular complications before 24–48 h after initiation of antiviral therapy
- Corticosteroids
  - topical, systemic to reduce intraocular inflammation, but does not reduce the severity of necrosis
  - oral prednisone 60–80 mg/day
- surgical treatment
  - early vitrectomy with laser treatment of areas of necrosis

Differential Diagnosis ARN (Table 14.1)

PORN Progressive Herpetic Retinal Necrosis

- It is a rapidly progressive necrotizing retinal syndrome [8]
- Clinical—multifocal necrotizing retinitis in the early stages followed by confluence of lesions, located in the middle periphery or posterior pole, with anterior or posterior progression
- Simultaneously there are other eye inflammations: iritis, hyalitis, vasculopathy with occluded vessels, associated with decreased central or peripheral vision

Table 14.1 Differential diagnosis

Starting	ARN	CMV
– Multifocal	– Multifocal	– Single focus
– Non-granular edge	– Well defined edges	– Granular edges
– Non-extensive haemorrhages	– Important vasculitis	– Variable hemorrhages
– Vitritis—rarely	– Important vitritis	– Few cells in the vitreous
– Painless	– Red, painful eye	– Painless
– Bilateral > unilateral	– Unilateral >bilateral	– Unilateral > bilateral
– Extremely fast progression	– Progression	– Slow progression
– Peripheral > central	– Peripheral >> central	– Peripheral or central
– Decreased vision (widespread)	– Central VA preserved	– Decreased vision
– VZH, HSV1, HSV2	– HZV, HSV, HSV2, CMV	– CMV

Treatment [9]
- Aciclovir—iv—2 weeks, continued with aggressive oral acyclovir to limit recurrences
- Foscarnet, Ganciclovir for vision preservation
- sometimes their combination with Aciclovir iv is necessary
  - initially foscarnet—60 mg/kg/day × 3/day with ganciclovir—5 mg/kg/day followed by
  - foscarnet—120 mg/kg/day and ganciclovir—5 mg/kg/day associated with
  - ganciclovir and intravitreal foscarnet
  - These combinations would do well in PORN.

CMV Retinitis

- CMV infects adults and is transmitted by contact with individuals excreting the virus, through urine, saliva, other secretions
  - CMV retinitis is common in AIDS patients [10]
- Clinical
  - CMV retinitis by diffusion of the virus along the nerve fiber layer, with retinal necrosis
  - there are two forms of retinal necrosis according to location and clinical appearance

    hemorrhagic form—fulminant, with intraretinal hemorrhages, with retinal necrosis in the vicinity of the vessels, in the posterior pole, with destruction of the retina in 6 months
    the painless granular form with slow progression, with little or no bleeding
  - retinal necrosis is replaced by glial scarring, with RPE alteration and fine pigmentation
  - minimal, moderate anterior vitreous and uveal inflammation

Treatment [9]
- Ganciclovir—intravenous, intravitreal, intravitreal implant, orally
- Valganciclovir
- Foscarnet—intravenous, intravitreal
- Cidofovir—intravenously
- Famivirsen—intravitreal

HIV Infection

- 80% of patients with HIV infection have microangiopathy with retinal lesions producing retinopathy with generally severe retinal vasculitis

- transplacental transmission of rubella virus in the first trimester of pregnancy
- ocular
  - "salt/pepper" type pseudopigmentary retinopathy more important at the level of the macula
  - iritis, iris atrophy
  - nuclear cataract

    microphthalmia
    interstitial keratitis
    optic neuropathy
    strong ametropia

- Opportunistic infections frequently caused by viral infections [11]
- ocular
  - arteriolar vasculitis
  - nodular syphilitic chorioretinitis
  - multifocal TB chorioretinitis
  - fungal chorioretinitis
  - CMV retinitis
  - viral retinal necrosis HSV, VZV with ARN syndrome, PORN
  - conjunctival lymphoma
  - Kaposi's palpebro-conjunctival sarcoma
  - viral bacterial keratoconjunctivitis
- treatment—Ganciclovir or Foscarnet
- Acyclovir for HSV, VZV

Parasitic Retinal Infections

Toxoplasmosis

- Ocular toxoplasmosis is a frequent cause of infection of the posterior segment of the eye and can be produced by the recurrence of a congenital infection, but more commonly by secondary infection in immunosuppressed patients [12].
- Clinical
  - retinochoroiditis with white, thick foci, foci associated with vitreous opacification (the retina is difficult to see through fog)
  - unilateral retinitis located in the vicinity of a pigmented scar (satellite lesions)
  - intense iridocyclitis
  - cataract
  - optic atrophy
- Complications

  - direct involvement of the macula and papillomacular bundle, papilla and large vessels
  - indirect macular damage through RD or fibrosis
- Systemic
  - congenital form: convulsions, hydrocephalus, intracranial calcifications, deafness
- Treatment
  - toxoplasmic retinochoroiditis can be self-limiting
  - treatment is indicated in:

    severe recurrent forms of toxoplasmic retinochoroiditis
    in forms with peripapillary macular localization, associated with severe vitritis
    persistence of the disease for more than a month

The classic treatment is:

- Combined [9, 13]
  - pyrimethamine
  - sulfadiazine with
  - corticosteroids to reduce inflammation
- pyrimethamine 75–100 mg/day on day 1 followed by 25–50 mg/day for 4–6 weeks depending on clinical response (may produce leukopenia and thrombocytopenia)
- sulfadiazine 2–4 g followed by 1 g × 4/day for 4–6 weeks
- folinic acid associated with pyrimethamine therapy
  - or alternatively
- trimetropin/sulfamethoxazole 160/180 mg × 2/day associated with corticosteroids
  - clindamycin is an effective alternative in case of allergy to sulfonamides
  - clindamycin may be combined with sulfadiazine pyrimethamine and corticosteroids in macular and/or ON lesions with significant vitreous clouding and large VA decrease.
- oral clindamycin 500 mg × 4/day—4 weeks with side effects: colitis, diarrhea
  - Atovacuone—indicated as primary therapy in moderate episodes of Pneumocystis carini pneumonia in patients with toxoplasma
  - Azithromycin with pyrimethamine plus sulfadiazine, but with side effects
  - Corticosteroids 60–80 mg/day for 2–6 weeks to reduce vitreous inflammation and CME

    the corticoid is necessarily associated with the systemic antimicrobial agent

topical corticosteroids or subconjunctival injections in anterior uveitis

Toxocariasis

It is the systemic infection with larva migrans of toxocara canis (in dogs) with ocular manifestations [14]:

- Solitary posterior pole retinal granuloma
  - Onset 6–14 years with unilateral vision loss
  - Clinical—single retinal granuloma
  - Complications:

    retinal folds
    vascular distortions
    RD

- Peripheral granuloma
  - onset in adolescence, or adult with decreased VA by traction, sometimes asymptomatic
  - Fundus—white, round, hemispherical peripheral granuloma the size of the optic disc (or larger)
  - Scarring with fibrous traction bands in vitreous towards pars plana, papilla
  - Complications

    macular heterotropia, pseudostrabismus
    tractional RD

- Chronic endophthalmitis
  - Onset between 2–9 years with leukocoria, strabismus, unilateral vision loss
  - Clinical

    anterior uveitis sometimes with intense anterior chamber reaction
    vitreous inflammation
    exudative RD
    vitritis with inflammatory traction bands

  - Complications

    posterior subcapsular cataract
    glaucoma
    leukocoria
    phthisis bulbi

  - hypereosinophilic

Treatment

- Anthelmintic: Thiabendazole, Aldendazole, Mebendazole, Diethylcarbamazine
- Associated corticosteroids: Thiabendazole 50 mg/kg/day—7 days plus, Prednisolone 0.5–1 mg/kg/day
- Topical—steroids, mydriatic

Choroidal Pneumocystosis

It is the opportunistic infection with pneumocystis carini, a major cause of mortality and morbidity in AIDS

- Most patients with choroiditis have aerosolized pentamidine in the prophylaxis of P. carini pneumonia
- The existence of choroiditis signifies the seriousness of the vital prognosis

Fundus—round, yellowish, bilateral, asymptomatic choroidal lesions
Treatment: Bactrim: iv, Pentamidine iv

Mycotic Retinal Infections

Fungal Choroiditis

- Cryptococcal choroiditis is cryptococcal neoformans infection frequently associated with meningitis in AIDS patients
- Fundus
  - multifocal choroiditis with occasional extension to the retina and papilla
  - endophthalmitis—rare
- Treatment
  - Amphotericin B—iv
  - Vitrectomy with intravitreal injection of amphotericin

Systemic and Ocular Inflammatory Pathology (Etiology)

Vasculitis [2]

- *periarteritis nodosa*
- *Wegener's granulomatosis*
- *Horton's disease*
- *Behcet's disease*

- *Takayasu's disease*
- *Eales disease*
- *Multiple sclerosis*

Other causes of retinal vasculitis: TB, borreliosis (Lyme disease), listeria, syphilis, viruses

Behcet's Disease

It is an HLA-B51-associated idiopathic hemorrhagic vasculitis with genetic predisposition in Japanese of probably autoimmune cause

Diagnostic Criteria [2]

Major criteria	Minor criteria
– Aphthous oral ulcerations – Skin lesions – Genital ulcers – Uveitis – Complete Behcet—4 major criteria simultaneously or over time – Incomplete Behcet—3 major criteria simultaneously or over time or uveitis and one major criterion – Suspected Behcet—2 major criteria – Possible Behcet—1 major criterion	– Arthritis – Gastrointestinal injuries – Epididymitis – Vascular diseases – Neuropsychic symptoms

The disease progresses with multiple acute episodes and periods of remission of variable duration

Ocular

- acute recurrent nongranulomatous anterior uveitis with hypopyon and multiple posterior synechiae.
- posterior uveitis
- retinitis with dispersed retinal infiltrates
- periphlebitis and periarteritis
- papillary edema
- massive retinal exudate
- occlusive vascular disease
- CME
- End-stage with: optic atrophy, chorioretinal scars, obstructed thin arteries

Treatment

- topical/parabulbar/systemic corticosteroids
- in unresponsive patients:
  - colchicine
  - immunosuppressants: chlorambucil, ciclosporin, interferon α

- **Disseminated lupus erythematosus**
  - Ocular

    vascular occlusions
    ischemic retinopathy
    blepharitis
    keratoconjunctivitis
    ischemic choroidopathy
    oculomotor paralysis

- **Sarcoidosis**
  - Ocular

    exudative retinopathy
    ischemic retinopathy
    granulomatous uveitis

Choroidal White Spots Syndrome [2]

- Sympathetic ophthalmitis
- Vogt-Koyanagi-Harada syndrome
- Internal punctate choroidopathy
- Multifocal choroiditis with panuveitis
- MEWDS
- Serpiginous choroiditis
- Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)
- Birdshot retinochoroiditis
- Sarcoidosis

Sympathetic Ophthalmitis

- Bilateral granulomatous panuveitis occurring after penetrating eye trauma accompanied by uveal membrane herniation
  - onset between 2 weeks and 3 months after trauma with photophobia in the second eye
  - clinical

    bilateral chronic granulomatous anterior uveitis
    bilateral multifocal choroiditis

  - treatment

    systemic corticosteroids improve the long-term prognosis

enucleation on the traumatized eye is sometimes necessary, but NOT after the onset of sympathetic ophthalmia

Vogt-Koyanagi-Harada Syndrome

Idiopathic multisystem disorder affecting pigmented individuals (Japan) characterized by: alopecia, vitiligo, poliosis and CNS involvement.

- Ocular
  - chronic granulomatous anterior uveitis, bilateral—Vogt-Koyanagi syndrome
  - bilateral posterior uveitis with:

    multifocal choroiditis
    exudative retinal detachment

Internal Punctate Choroiditis

Bilateral multifocal chorioretinal disease **without inflammatory phenomena** in myopic women 40–50 years old, with poor prognosis

- onset 40–50 years with photopsia
- Fundus—multiple deep spots with irregular outline, located in the posterior pole
- Similar lesions affecting the second eye
- well-defined scars after a few weeks, bilaterally
  - complications: foveal scar, choroidal neovascularization

CNV Treatment
- FC laser
- systemic corticosteroids
- surgical excision of subfoveal CNV in some cases

Multifocal Choroiditis with Panuveitis

Bilateral, chronic, recurrent condition with poor prognosis, with lesions and scarring similar to acute histoplasmosis.

- onset at 40–50 years with: photopsia, floating bodies, blurred vision
- clinical
  - anterior uveitis in 50% of cases with hialitis
  - small deep yellow-gray spots in posterior pole and periphery
  - inactive lesions with clear margins and pigmentation
- Complications

  - Direct damage to the fovea
  - CNV
  - OMC
  - subretinal fibrosis
- Treatment
  - Immunosuppressants associated with corticosteroids
  - Laser photocoagulation for CNV
  - Anti-VEGF
  - Pars plana vitrectomy eith pelling for epiretinal membranes
- Differential diagnosis: sarcoidosis, histoplasmosis, internal punctate choroidopathy

Multiple Evanescent White Dot Syndrome—MEWDS

Unilateral, self-limited condition, with a favorable prognosis, in 30–50 years old patients

- onset with sudden decrease in vision, sometimes associated with photopsia
- clinical
  - discrete hialitis
  - numerous small deep white spots in posterior pole NOT affecting the fovea (late hyperfluorescence)
  - papillary edema and macular enlargement
- ERG—reduction of the "a" wave
- Rapid evolution to spontaneous resolution within weeks with persistence of foveolar granulation.

Serpiginous Choroiditis

Asymmetric, progressive bilateral disease with recurrent whitish macular and peri-papillary lesions, associated with scarring, accompanied by paracentral scotoma and decreased vision in 40–60 year olds patients

- onset with recurrent episodes of choroiditis, RPE hypertrophy and chorioretinal atrophy with cessation of vision and metamorphopsia
- clinical
  - anterior uveitis, hialitis
  - fundus

subretinal infiltrates with blurred borders in the vicinity of the papilla and macula that expand (serpentine) and are accompanied by hyperpigmentation and recurrence of lesions at the periphery of scars
significant chorioretinal atrophy
extensive cicatricial lesions

- Subnormal EOG
- prolonged evolution in years
- complications:
  - macular damage
  - CNV
  - subretinal fibrosis
- differential diagnosis: sarcoidosis, syphilis, non-Hodgkin's lymphoma
- treatment
  - tritherapy with systemic corticosteroids, azathioprine and ciclosporin
  - early cyclosporine monotherapy (sometimes)
  - laser photocoagulation (CNV)
  - VEGF
  - PPV

Acute Retinal Epithelitis

Self-limited disease with a good prognosis, unilateral in 75% cases, at 30–50 year old patients with a sudden decrease in central vision.

Acute Posterior Multifocal Placoid Pigment Epitheliopathy (APMPPE)

- APMPPE is an acquired inflammatory disease that affects the retina, retinal pigment epithelium, and choroid in otherwise healthy young adults.
  - is self-limiting

Clinical

- multiple white-yellow subretinal placoid lesions of the posterior pole, frequently bilateral and in various evolutionary stages:
- remission in a few weeks to a few months, with cicatricial areas circumscribed at the level of the retinal pigment epithelium.
- Visual acuity can be significantly impaired if the macula is involved, but **recovery is the rule**, with or without therapy, with up to 80% of affected eyes regaining an acuity of 20/40 or better.

Treatment
- The treatment of APMPPE is controversial.
- Possible self-limiting resolution without treatment.
- Systemic steroids or biologic agents such as tumor necrosis factor inhibitors (infliximab) in cases involving significant visual impairment, those with debilitating recurrence, or cases involving systemic disease.

Birdshot Retinochoroiditis

Chronic, bilateral condition with poor prognosis, associated with vitritis and vasculitis, with decreased VA by CME, that affects 60–70 years old patients, with HLA-29 present (90%)

- onset with: blurred vision, floating bodies, nyctalopia
- clinical:
  - anterior uveitis and discrete hialitis
  - ill-defined subretinal ovoid lesions, cream-colored, with papillary hyperfluorescence, with different localizations: macula (constant/inconstant), inferonasal, middle periphery
  - inactive lesions with well-defined atrophic white spots
- evolution—self-limited evolution with preservation of vision—20%
- chronic evolution with decreased VA—80%
- complications: CME, epiretinal gliosis, CNV
- Treatment: corticosteroids, cyclosporine
- Differential diagnosis: sarcoidosis, TB, non-Hodgkin's lymphoma

Sarcoidosis

Idiopathic granulomatous disease affecting multiple organs, in which pulmonary involvement is predominant.

Ocular
- anterior uveitis
- acute in a young adult with sarcoidosis, with a brutal onset
- chronic—granulomatous in an older patient with chronic pulmonary sarcoidosis
- other manifestations: damage to the lacrimal glands, conjunctiva, sclera (nodules)
- affecting the posterior pole
  - retinal periphlebitis: focal, perivenous exudates, can cause venous branch occlusions
  - granulomas—choroidal, retinal, papillary, preretinal (Landers sign)
  - peripheral retinal neovascularization

intermediate uveitis

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Chapter 15
Ophthalmological Pathology of the Eye: Retinal Vasculitis

Marieta Dumitrache

Abstract **Vasculitis** are heterogenous group of diseases characterised by inflammation and necrosis of the vascular wall of artery anterior, vein, capillary, venule. **Temporal arteritis Gyant cell-arteritis Horton** is a chronic inflammation of the carotid and branches. The basic medication is systemic corticoid treatment. **Wegener granulomatosis** affect is the respiratory system, sinuses, kidney, orbit; is necessary treatment with cyclophosfamid. **Syndrome Churg Strauss** is a systemic necrotising vasculitis with granulomatosis inflammation associated with bronhial asthme, gromerulo renal and occular granulomas conjunctival, scleral, orbital, retinal. Combination of prednison with azathioprine can reduce morbidity in vasculitis.

Keywords Vasculitis · Gyant cell arteritis · Wegener granulomatosis · Churg Strauss syndrome

Retinal Vasculitis

- Vasculitis are a heterogeneous group of diseases, characterized by inflammation and necrosis of the vascular wall, which can affect any blood vessel: artery, arteriole, vein, capillary venule
  - inflammation of the vascular wall narrows the caliber and generates tissue necrosis
- Classification of vasculitis [1, 2]
  - vasculitis are:

    primary (of unknown cause)
    secondary to drug treatment, a toxin, infection, immune or other disease

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  - vasculitis may be limited to one organ or system or may be multisystemic.
  - vasculitis can be classified according to the size of the predominantly affected vessels [3].

- **Affecting large vessels—the aorta, its branches**
  - ***giant cell arteritis***—GCA
  - ***Takayasu's disease***—in people under 50 years old
- **Affecting the medium vessels—the main visceral arteries: renal, coronary, hepatic, mesenteric**
  - ***polyarteritis nodosa***
  - ***Kawasaki disease in children***
  - ***isolated vasculitis*** *limited* to a single organ or polyangietic overlap syndromes
- **Affecting small-caliber vessels (small arteries, precapillary arterioles, capillaries, venules, postcapillaries), with two clinical forms separated according to the presence of immune markers—ANCA—autoantibodies against the cytoplasm of neutrophils and monocytes** [4, 5]:
  - ANCA—negative vasculitis
  - ANCA-positive vasculitis with three primary necrotizing vasculitis on a small vessel
  - ***Granulomatosis with polyangiitis—Wegener's granulomatosis—GPA***

    necrotizing, granulomatous inflammation frequently located on the respiratory tract
    frequent necrotizing glomerulonephritis
  - ***Eosinophilic granulomatosis with polyangiitis—Churg Strauss syndrome—EGPA***
  - ***Microscopic polyangiitis***

    necrotizing vasculitis with/without minimal immune deposits, without granulomatous inflammation
    necrotizing glomerulonephritis
    pulmonary capillaropathy
- There is a genetic predisposition in all these diseases

The major symptomatology in vasculitis is related to the vascular localization involved in the inflammatory process, the age of the disease and the evolution of the inflammation towards tissue necrosis

- Tissue biopsy can confirm the diagnosis, but must be limited because the vasculitis is segmental or focal.
- At retinal level—vasculitis affects retinal arterioles—arteritis, veins—phlebitis or both—periphlebitis [3].
- Clinical—the fundus examination reveals vascular blockages, hemorrhages

Management in Vasculitis

- Oral steroids—moderate doses—200 mg/day orally, associated with H2 blocker—ranitidine (Zantac) 150 mg orally
- Topical steroids—prednisolone, acetate 1%
- Cycloplegic in the presence of anterior segment inflammation
- Injectable steroid under Tenon (triamcinolone 40 mg/ml)
- Cyclosporine 2–7 mg/kg/day or immunosuppressive agents in refractory forms.

Temporal Arteritis—Giant Cell Arteritis

- It is the chronic inflammation of the large vessels—the carotid and its branches, a more common condition in women over 55 [3, 6].
- Laboratory examination—shows signs of inflammation with
  - ESR, CRP—increased
- Clinical
  - headache
  - vision impairment
  - pain when chewing
  - fever
  - weight loss
  - asthenia
  - temporal artery sensitive to palpation
  - ESR very high
  - positive diagnosis confirmed by temporal artery biopsy
- Ocular
  - AAION—arteritic anterior ischemic optic neuropathy
  - Various visual disturbances

    Amaurosis fugax
    diplopia
    scotoma
    ptosis
    foggy vision

  - pain in the masseters (intermittent claudication), in the scalp.
  - **Treatment should be started as soon as temporal arteritis is suspected, and then the biopsy that confirms the diagnosis is done, so that the eye disease does not become bilateral** [7].
  - The basic medication is systemic corticosteroid treatment with prednisone 60 mg/day as a single dose for 2–3 weeks [2, 7]

if symptoms improve cortisone is tapered according to individual response
by 5–10 mg/day per week to 10–20 mg/day then by 1 mg/day per week
if symptoms recur when prednisolone is tapered, increase the dose
many patients need low doses of cortisone—years
in the presence of adverse effects of corticotherapy, AZATIOPRINE and METOTREXATE, INFLIXIMAB are used

Takayasu Arteritis

- Pulseless disease, aortic arch syndrome

Occlusive Thrombo-aortopathy

It is a rare condition, an inflammatory disease affecting the aorta and its branches that occurs commonly in adolescents, young women 8/1 and Asians [6, 8]

- **Clinical signs are related to vascular ischemia**
- Ocular
  - scleritis
  - amaurosis fugax
  - ocular ischemia
  - AION

Medical treatment requires:

- Corticosteroid therapy that can improve disease and reduce long-term vascular complications
  - Treatment with prednisone 60 mg/day orally, months, years, is gradually reduced according to the clinical evolution
  - Methotrexate in refractory cases
- In corticosteroid-resistant cases—METHOTREXATE, CYCLOPHOSPHAMIDE, AZATIOPRINE

Polyarteritis Nodosa—Periartheritis-Pan

- It is a systemic necrotizing vasculitis located in the medium and small arteries at the arterial bifurcations with secondary tissue ischemia [9]:
- Proliferation of the vascular intima occurs with thrombosis and occlusion that causes infarction

- The integuments, peripheral nerves, liver, heart and digestive tract are most frequently affected
  - the pulmonary arteries are not affected
  - the kidney can show ischemia with glomerular infarction
  - massive infarcts (rarely) or areas of focal hepatic capsular vasculitis may occur in the liver
- Affection is more common in men
- Nonspecific signs and symptoms [10]
  - fever
  - weight loss
  - abdominal pain
  - hypertension
  - edema
  - biopsy and arteriography are required for diagnosis
- Ocular
  - keratoconjunctivitis sicca
  - necrotizing sclero keratitis
  - retinal vascular occlusions
  - AION
  - retinal vascular aneurysms (rare)
  - damage to the superior oblique tendon
- General
  - heart damage: myocardial infarction, hypertension, pericarditis, angina
  - kidneys: nephritic or nephrotic syndrome
  - intestines: heart attack, abdominal pain
  - peripheral neuropathy
  - arthritis, myalgia
  - CNS—headache 20%, convulsions 10%
  - skin lesions: purpura, subcutaneous nodules
  - **Initial treatment must be aggressive to achieve clinical remission, untreated acute or chronic disease is fatal through failure of vital organs, cardiac, renal, digestive** [11, 12]
  - the treatment must be administered for a long time and the evolution of the disease can be complicated by the adverse effects of the drugs administered
  - if the patient does not respond to corticosteroid treatment in an adequate dose of 60–80 mg/day prednisone, for 3–4 weeks immunosuppressive treatment with:
- CYCLOPHOSPHAMIDE—2–3 mg/kg/day with dose adjusted to maintain peripheral blood WBC > 3000.
- AZATIOPRINE, METHOTREXATE

Kawasaki Disease

It is an idiopathic vasculitis with predominantly mucocutaneous manifestations that affects children around 5 years of age in Japan [13]

- can be fatal 1–2%
  - Ocular

    bilateral acute conjunctivitis (90%)
    superficial punctate keratitis
    medium anterior uveitis, nongranulomatous (80%)
    retinal periarteritis
  - Sistemic

    fever for more than 5 days
    oral lesions—erythema, fissures, strawberry tongue
    skin rash
    cervical lymphadenopathy
    affecting the extremities: edema, erythema, desquamation
    associated with polyarteritis
    the temporal arteries may be affected

Complications—coronary arteritis 15%.

Induction treatment with high doses of IV immunoglobulins and aspirin can reduce coronary risk and death

- In some cases (well chosen) methylprednisone can be effective in reducing fever.

Maintenance treatment is not necessary, knowing that the disease is self-limiting:

- possible coronary abnormalities can be treated with aspirin (low doses 80–120 mg/day), anticoagulants, beta-blockers.

The recommendations of the European League against Rheumatism for the treatment of ANCA vasculitis (Table 15.1)

Granulomatosis with Polyangeitis—GPA

Wegener's Granulomatosis [14]

Rare condition with onset of granulomatous inflammation of the mucosa of the upper and lower respiratory tract, progressing to generalized necrotizing granulomatous vasculitis and glomerulonephritis [15, 16]

Table 15.1 Treatment in ANCA vasculitis

Vasculitis	Induction treatment	Remission maintenance treatment
Localized	Methotrexate + STEROIDS	STEROIDS (low dose) + – AZOTHIOPRINE – LEFLUNOMIDE – METHOTREXATE
Initial systemic		
WIDESPREAD	CYCLOPHOSPHAMIDE (oral/iv) + STEROIDS	
Severe	ADDITIONAL – PLASMAPHERESIS	
Resistant cases	– IMMUNOGLOBULIN iv – MOFETIL MYCOPHENOLATE RITUXIMAB PLASMAPHERESIS	

- **Granulomatous inflammation affects the respiratory system, sinuses, kidney, orbit**
- Clinical diagnosis for GPA—two of the following
  - oral, nasal inflammation with painful ulcers/or not, purulent or bloody rhinorrhea
  - pulmonary—nodules, paremchymatous infiltrates, cavities
  - microhematuria (>5 red blood cells per field in sediment, cylinders, red blood cells)
  - biopsy—granulomatous inflammation of the arterial wall, perivascular, extravascular
- Ocular
  - painful proptosis
  - painful ophthalmoplegia
  - chemosis
  - conjunctivitis
  - necrotizing scleritis, episcleritis
  - keratitis
- Fundus
  - cotton wool spots
  - thin arteries
  - tortuous veins
  - ON edema
  - thickened choroid
  - CME
  - CRAO
  - lacrimal-nasal duct obstruction
- General

  - hemoptysis
  - renal insufficiency
  - cerebral vasculitis
  - weight loss
  - peripheral neuropathies
  - fever
  - arthralgia
  - saddle nose by destroying the nasal vessels
- ANCA (+) 6–7%
- If the diagnosis is posed early, the current treatment allows the remission of the disease and the reduction of renal complications.
  - **Cyclophosphamide 2mg/kg/day is the drug of choice**

    Cyclophosphamide is administered one year after achieving clinical remission;
    The daily dose is reduced by 25 mg every 2–3 months

Eosinophilic Granulomatosis with Polyangiitis—Churg Strauss Syndrome—EGPA

- It is a systemic necrotizing vasculitis with granulomatous eosinophilic inflammation which frequently affects the airways and small and medium-sized vessels, associated with bronchial asthma, possible glomerular renal damage [17, 18]
- Systemic
  - bronchial asthma
  - eosinophilia >10%
  - mono or polyneuropathy
  - migratory pulmonary infiltrates
  - abnormalities of the paranasal sinuses
  - biopsy—extravascular eosinophilic accumulation
- Ocular
  - conjunctival granulomas
  - scleritis
  - orbital inflammation
  - retinal periarteritis
- Treatment of ANCA positive small vessel vasculitis (Wegener, Churg-Strauss)
  - induction treatment is done with CYCLOPHOSPHAMIDE iv in a high dose or orally in a lower dose associated with the administration of CORTICOIDS [8, 19, 20]

– maintenance treatment after achieving remission is continued for 24 months with prednisolone 10 mg/day, and discontinuation after 6–18 months to 2 years depending on therapeutic response

combination of prednisolone with azathioprine can reduce morbidity in vasculitis

they have also been used in the treatment of vasculitis [21]

TNFα inhibitors in acute disease
INFLIXIMAB
RITUXIMAB (IgG monoclonal antibody) with B-cell destruction induces disease remission
IMATINIB—inhibits T cells and proliferation

Biological Therapy in Vasculitis

- In vasculitis, inflammation occurs with destructive organ damage through the interaction of ANCA with neutrophils and endothelium [22, 23].
  - Biological agents can be used to block mediators and effectors of inflammation

Fighting inflammation by inhibiting it by binding to TNFα

ETANERCEPT—ENBREL
INFLIXIMAB—REMICAD
ADALIMUMAB—HUMIRA

The final effect in reducing the migration and activation of neutrophils

- Anti-ANCA therapy, which interferes with ANCA binding to epitopes
- HUMAN IMMUNOGLOBULINS prevent ANCA-mediated activation of neutrophils
- Treatment against B cells
  - RITUXIMAB—MABTHERA achieves depletion of B lymphocytes
  - BELIMUMAB—inhibits the maturation of B cells
- Treatment against T cells
  - ABATACEPT—ORENCIA—inhibits the activation of T lymphocytes
  - ALEMTUZUMAB—CAMPATH—destroy T cells

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Chapter 16
Ophtalmological Pathology and Management in Eye Disease: non Age Related Macular Degeneration (AMD) Pathology

Marieta Dumitrache

Abstract **Inflammatory macular** disease are Central serous chorioretinitis (CSR), serpiginous choroiditis, Birdshot retinochoroiditis. **Macular hole** can be: idiopatic 80%, secondary in myopia with posterior staphyloma posttraumatic, postoperator (Diabetic retinopathy). **Degenerative myopia** has ocular posterior staphyloma, rupture of Bruch membrane, cataract, glaucoma, corioretinal artrophy, Foerster Fuchs spot macular hemorrhage, retinal holes, neovascularisation. **Angioid streacks** is recessive hereditary degenerative of the Bruch membrane with rupture of the elastic layer, with reserved prognosis. **Macular edema** is present in: retinopathy diabetic, malignant hypertension, Central retinal Vein Obstruction (CRVO), Coats disease, Irvine-Gass disease, after cataract surgery. **Macular cystoid** edema etiologic: pars-planitis, Goldman Favre, prostaglandin. **Epimacular membrane** can be idiopathic or secondary in Vitreal Hemorhage. **Toxic maculopathy** with clorochin, phenotiazine, interferon. **Traumatic maculopathy** are edem Berlin, choroidal tears, macular hole, Purcher retinopathy, Therson syndrome.

Keywords CSR macular hole · Degenerative myopia · Angioid Streacks · Macular edema · EMC · Toxic maculopathy

Acquired Macular Disorders

- INFLAMMATORY MACUAR DISEASE
  - central serous chorioretinopathy

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- DEGENERATIVE MACULOPATHIES
  - Age-related macular degeneration
  - Age-related macular hole
  - Myopic macular degeneration
  - Angioid streaks
- VARIOUS MACULOPATHIES
  - Macular edema
  - Cystoid macular edema
  - Macular epiretinal membrane
  - Macular Pucker
  - Choroidal folds
  - Choroidal vasculopathy
  - Maculopathy and congenital coloboma of the papilla
- TOXIC MACULOPATHY
  - Antimalarials
  - Hydroxychloroquine
  - phenothiazines
  - crystalline
- MACULOPATHY IN METABOLIC DISEASES
  - Diabetic maculopathy
  - Maculopathy in sphingo-lipidoses
- TRAUMATIC MACULOPATHY
  - Berlin edema
  - Choroidal tears
  - Purcher retinopathy
  - Valsalva retinopathy
  - Terson syndrome
  - Abused newborn syndrome

Inflammatory Macular Disease

Central Serous Chorioretinitis (CSR)

- *CSR is characterized by* spontaneous serous detachment of the neurosensory retina in the macular region on a choriocapillary leakage area through the retinal pigment epithelium (RPE) with or without detachment of the retinal pigment epithelium [1].
- Affects young man, 10/1, 30–40 years, anxious, unilateral (rarely bilateral) [2].
- Predisposing factors: emotional stress, hypertension, SLE, systemic corticosteroid therapy, organ transplant, Cushing.

- Onset with relatively unilateral positive scotoma, micropsia, metamorphopsia, slight change in VA [3].
- symptoms
  - relatively positive, central, unilateral scotoma and micropsia
  - decrease in vision to 1/10, improved by adding converging lenses "pseudohypermetropia induced by macular prominence given by macular edema.
  - Micropsia
  - Dyschromatopsia
  - Asymptomatic
  - Abnormal Amsler test
- ophthalmoscope
  - oval or round, single or multiple superficial elevation (bubble) in the macular area given by the retinal sensory take-off of dark pink color;
  - annular, circular reflex that bounds the bubble as a bright halo;
  - small yellowish precipitates on the surface of the bubble after 1–2 weeks;
  - absent foveolar reflex
  - sometimes atrophic PE
  - Corhoidal Neo Vascularization very rare
- Fluoresceine Angiography (FA)
  - small spots of early hyperfluorescence in the elevation's area, growing vertically, with lateral extension with a "smokestack" or "fire in the fog" appearance;
  - late hyperfluorescence with dye diffusion into the bubble through the "vanishing point".
- Variable recurrences and/or bilateralization are possible.
- Evolution
  - spontaneous resolution in 6 months without visual sequelae;
  - spontaneous resolution within 12 months with moderate visual degradation (rare);
  - persistence more than 1 year with PE alteration (very rare).
- Complications
  - neovascular choroidal membranes (rare) through numerous recurrences;
  - macular edema;
  - chorioretinal atrophy.
- Treatment
  - Clinical follow-up and FA because 80–90% have spontaneous resolution, with VA returning to normal in 4–12 weeks;
  - **The use of corticosteroids in the treatment of CSR should be avoided as it may lead to exacerbation of already existing serous detachments.**

- Intravitreal bevacizumab (Avastin) has been used to successfully treat rare complications of choroidal neovascularization after CSR [1, 4].
- Laser photocoagulation [5]
- *indications*:

  prolonged course of the disease beyond 4 months in patients with decreased vision
  Recurrent CSR with decreased vision
  affecting the second eye
  there is cloudy subretinal fluid
  the professional need or other needs of the patient that require the rapid recovery of vision.
  patients with recurrent episodes of serous detachment, with diffusion located more than 300 μm from the center of the fovea.
  laser treatment shortens the course of the disease and reduces the risk of CSR recurrence, but does not appear to improve the final visual prognosis.
  photodynamic therapy (PDT) for acute and chronic CSR

- *technique*—low or moderate "vanishing point" impacts after FA 200 μm/0.2 s
- *complications* of photocoagulation are more frequently related to technical errors: retinal hemorrhages, foveolar burns, CNV, retraction syndrome.

Degenerative Macular Disease

Age-related Macular Degeneration

Age-related Macular Hole

- A macular hole is a retinal hole in the fovea and is produced by progressive tangential vitreoretinal traction on the fovea, with the onset of unilateral central vision loss (sometimes an accidental discovery), which more commonly affects women after 60 years. 3/1, bilateral 25–30% [6, 7].
- The most common macular hole is senile (idiopathic 80%, but it can develop after: trauma, post-surgery, CME, post-inflammatory.
- A macular hole can be:
  - idiopathic 80%;
  - secondary: strong myopia with posterior staphyloma, post-traumatic, post-eye surgery (RD), ischemic retinal vascular diseases, VH, CME, treatment with pilocarpine Best's disease.

Onset with unilateral, central vision loss, often discovered incidentally or may manifest as metamorphopsia and VA reduction.

- symptoms
  - Metamorphopsia
  - Decreased central vision
  - Absolute central scotoma, relative.
- Ocular signs are different depending on the clinical stage [8].
  - stage 1—impending macular hole

    1a—foveolar yellow spot (intrafoveolar cyst)
    1b—occult macular hole—yellow ring at the interface with the vitreous cortex
  - stage 2—early hole—yellow ring widening and dehiscence—pseudo-operculum
  - stage 3—full-thickness hole with a central round opening attached to the posterior hyaloid ± pseudo-operculum
  - stage 4—full-thickness hole surrounded by a ring of subretinal fluid with yellowish deposits at the base of the crater and complete PVD.
- GASS classification [9]
  - central yellow spot, with effacement of the foveolar depression and vitreous attached to the fovea (intrafoveolar cyst)
  - yellow ring at the vitreous cortex interface
  - round or oval, crescentic or horseshoe retinal defect, with/without operculum (early hole), with tear in the ceiling of the macular hole with full-thickness defect.
  - round central retinal defect, diameter ≥400 μ, surrounded by hypertrophic retina with/without prefoveal operculum, premacular vitreous
  - round central retinal defect, attached full-thickness retina with diameter ≥400 μ with premacular vitreous, detached prepapillary (Weiss ring) with/without operculum.
- The differential diagnosis between:
  - MH in the full thickness of the macular retina
  - Lamellar macular hole, involving only the inner layers, not the full thickness of the macular retina
  - Pseudohole: hole in ERM
- Watzke–Allen test—the narrow light beam projected onto the center of the hole appears interrupted and thinned
  - if macular hole helps to differentiate MH from pseudohole and lamellar hole.
- Laser beam test—50 μm spot projected in center of macular hole, spot disappears if MH.
- OCT—makes the stage diagnosis

- highlights the different stages of MH and the existence of other diseases
- highlights the retinal defect with or without traction at the edge of the hole
- can differentiate lamellar hole and macular cyst
- guides the treatment options and surgery, if necessary

- Differential diagnosis:
  - other macular holes: posttraumatic, in strong myopia
  - macular pseudohole.

Treatment

- Surgical treatment is not indicated in stage 0-1 because the hole may close spontaneously, but the patient should be monitored because 50% progress, requiring surgical treatment [10–12].
- Surgical treatment is indicated in:
  - Stages 2–4
  - VA below 5/10
  - MH for less than 1 year
- Surgical treatment consists of PPV with peeling of the internal limiting membrane and posterior hyaloid associated with gas or silicone packing for stages 2–4
- Stage 2a
  - the greatest post-surgical success is achieved if the operation is performed within the first 6 months

    postponing the operation beyond 1 year halves the chances of success
- Stage 2b—possible post-surgical complications:
  - increased hole size
  - cataract
  - RD
- Stage 3—PPV with ILM peel, gas injection, face down position
- MH < 400 μm with vitreomacular traction can be treated with intravitreal injection of 2.5 mg/ml **ocriplasmin (Jetrea)** with 50% chance of MH closure
- Prognosis:
  - Stage 1: MH may spontaneously close
  - Stage 2:

    without treatment VA decreases
    with treatment 90% of MH closes

Degenerative Myopia

- The progressive extension of the eyeball in high myopia can generate degenerative changes in the sclera, choroid, Bruch's membrane, PE and sensory retina (myopia over 6D, produces an axial elongation of around 25 mm).
- Degenerative lesions in myopia occur when the axial length of the eyeball increases above 20 mm and the dioptric value exceeds 6D [13]
- Degenerative myopia is more common in women and can reach up to 2% of the population.
- Myopia is pathological when it exceeds 8D and the axial length is ≥32.5 mm
  - Ocular [14, 15]

    Anterior segment

    thin sclera with posterior staphyloma and crisscrossing, irregular yellowish lines (through ruptures of Bruch's membrane)
    cataract
    glaucoma

    Fundus

    with tigroid appearance with RPE thinning and visibility of choroidal vessels; chorioretinal atrophy
    peripapillary chorioretinal atrophy (myopic cone) and in the posterior pole with posterior staphyloma in high myopia;
    ruptures of Bruch's membrane, in the form of irregular, crossed, branched yellow lines ± subretinal hemorrhages;
    subretinal hemorrhage frequently in the vicinity of the fissures
    temporal optic atrophy; optic disc elongated or oval, inclined, optic cup shallow
    Foerster-Fuchs spot—pigmented lesion following the resorption of a macular hemorrhage, with black spots due to RPE hyperplasia in the macula;
    retinal holes
    lattice degeneration
    RRD
    CNV (choroidal neovascularization)
    MH

    maculopathy

    RPE and choriocapillary atrophy
    CNV
    exudative maculopathy
    macular hole ± RD
    Foerster-Fuchs spot is a pigmentary lesion following the resorption of a macular hemorrhage.

- symptoms
  - blurred vision
  - metamorphopsia
  - scotoma
  - photopsia
  - RD through vitreous degeneration, giant tears.
- Myopia can be associated with:
  - Posterior or early subcapsular cataract
  - Increased incidence of POAG
  - RD through macular hole or peripheral dehiscence
- Complications
  - CNV in the vicinity of the fovea is present in 65% of cases and has a poor prognosis with significant loss of vision within two years
  - RD
  - MH
  - cataract
  - glaucoma

Treatment

- optical correction corresponding to the refractive error, with the help of aerial contact lenses after objective determination and subjective correction.
- CNV treatment [6, 16, 17]
  - Argon Laser photocoagulation
  - VEGF

    bevacizumab (Avastin)—1.25 mg
    ranibizumab (Lucentis)—0.5 mg
    aflibercept (Eylea)—2 mg with beneficial results
- The treatment of exudative maculopathy secondary to CNV associated with ruptures of Bruch's membrane is done by photodynamic therapy in the presence of retrofoveal CNV associated with strong myopia and if their surface is below 5400μm, or VA is >2.5/10.
- Treatment of RD, MH through efficient vitreoretinal surgery.
- Treatment of medical, surgical glaucoma depending on the type of glaucoma and degree of decompensation.
- Cataract surgical treatment with lens implant, if necessary depending on the amount of myopia.

Causal Treatment

- Polycarbonate protective lenses, because any trauma can cause hemorrhages or choroidal tears.
- Medical treatment of associated diseases.
- CNV treatment:

- photocoagulation, if CNV is extrafoveal;
- if CNV is subfoveal—intravitreal: bevacizumab (Avastin) 1.25 mg may be required.

Angioid Streaks (AS)

- AS—Groenblad—Strandberg disease—is a recessive hereditary degenerative condition of the Bruch's membrane, in which the rupture of the elastic layer occurs, through an abnormal fragility related to the degenerative process, with changes in the RPE and choriocapillaries.
- The syndrome can be idiopathic or associated with systemic disease 50% and includes [2, 18]:
  - Pseudoxanthoma elasticus—60%: skin folds in the neck, gastrointestinal bleeding, hypertension.
  - Paget's disease—(8%): extraskeletal calcifications, osteoarthritis, deafness, vertigo, increased alkaline phosphatase
  - Senile elastosis
  - Calcinosis
  - Abetalipoproteinemia
  - Thalasemia
  - Ehler-Danlos syndrome: blue sclera, hypersensitive joints.
- Systemic Associations (PEPSI)
  - **P** pseudoxanthoma elastic—the most common
  - **E** hlers—Danlos type 6—hyperextensible skin
  - **P** aget—increased alkaline phosphatase
  - **S** ickle cell—sickle cell disease and other hemoglobinopathies
  - **I** diopathic.
- symptoms
  - asymptomatic
  - blurred vision, over time decreased VA
  - metamorphopsia if CNV develops
  - scotoma
- fundus
  - bilateral reddish-brown linear striae, below normal retinal vessels, starting radially from the papilla with pigmentation around the striae
  - lesions with irregular lacy edges, sometimes temporally pigmented by the macula, "orange peel" appearance in patients with pseudoxanthoma elasticus, retinal pigmentation

    optic disc drusen
    hemorrhagic lesions after a minor trauma or after CNV

peripheral chorioretinal scars “salmon spots”

- subretinal hemorrhages
- RPE detachment
- macular degeneration
- central/paracentral scotoma if CNV develops.

- Prognosis—reserved if CNV develops

Treatment

- Polycarbonate protective lenses, because any trauma can cause hemorrhages or choroidal tears.
- Medical treatment of associated diseases.
- CNV treatment:
  - photocoagulation, if CNV is extrafoveal;
  - if CNV is subfoveal—intravitreal: bevacizumab (Avastin) 1.25 mg may be required.

Various Maculopathies

- **Macular edema—ME**
  - It occurs when the perifoveal capillaries become abnormally permeable and allow edema to accumulate.
  - Causes of ME: diabetic retinopathy, malignant hypertension, CRVO, Coats disease, Irvin Gass (after cataract surgery).
  - Causal treatment

    photocoagulation in DR, CRVO
    vitrectomy
    anti-inflammatory treatment, cortisone in uveitis.

Cystoid Macular Edema—CME

- CME occurs at the level of the macula and has a petaloid appearance.
- Cystoid macular edema is a painless condition characterized by thickening or distension of the central retina (the macula) and usually involves alteration of central vision by blurring or distortion of images. Less common symptoms are metamorphopsia, micropsia, scotomas and photophobia [19].
- CME is produced by a breakdown of the internal hematoretinal barrier, with accumulation of fluid between the external plexiform and internal nuclear layers and formation of honeycomb or flower petal-like microcysts [20]

– Multi-etiological condition, with possible remissions and exacerbations of CME, with VA decrease over time
– Etiological—DEPRIVEN

Diabetis
Epinephrine
Pars planitis
RP (retinitis pigmentosa)
Irvine Gass
Vein (occlusion)
E (prostaglandin)
N (nicotinic maculopathy)
Other: parafoveal telangiectasia, juvenile retinoschisis, Goldman—Favre, Xalatan

Causes of CME

- *Congenital CME in:*
- RP
- CME-AD
- familial exudative vitreous retinopathy
- *Acquired CME:*
  - CRVO
  - DR (diabetic retinopathy)
  - postoperative—after cataract surgery: Irvine Gass syndrome
  - uveitis
  - vitreomacular traction
  - drugs: nicotinic acid, prostaglandin analogues, epinephrine.
- CME following cataract surgery is usually self-limiting, however chronic CME with multiple recurrences can cause photoreceptor damage with permanent reduction in central visual acuity.
  - The main cause of cystoid macular edema (CME) depends on the underlying disease, but most pathogenic events relate to vascular instability and blood-retinal barrier breakdown. Retinal Müller cells become supersaturated with fluid and degrade [6].
- **Pathogenesis**
  - CME is produced by a breakdown of the internal hematoretinal barrier, which causes an accumulation of fluid between the outer plexiform and inner nuclear layers in microcystic spaces [6, 13]

    these microcysts can merge, sometimes it is possible to form a lamellar hole
- The onset of CME is variable depending on the cause with possible remissions and exacerbations, accompanied over time by a decrease in VA [20].
- symptoms

  - Decreased vision
  - Micropsia
- Clinical signs
  - The fundus examination reveals in the macula at the level of the foveola [3]

    decreased foveolar reflex
    cystic spaces in the foveolar region
    central xanthophyll pigment with yellowish punctate impregnation in the center of the fovea
    exudates
    folds at the fovea
    signs of uveitis or post-surgical complications: capsular tears, incarcerated iris, vitreous detachment
    cystic changes in the macula
- ASSESSMENT
  - full eye clinical examination, careful, biomicroscopic, ophthalmoscopic, FA
- FA
  - delimited cystic spaces
  - punctate early hyperfluorescence, perifoveal with late petaloid discharge
  - delayed ON head *leakage in Irvin-Gass syndrome*
- OCT
  - highlights cystoid intraretinal spaces
  - shows vitreomacular traction

Medical Treatment [9, 11, 17]

- Careful monitoring of aphakic and pseudophakic patients.
- Postoperative control of ocular inflammation
- ***Steroidal anti-inflammatories***
  - Corticosteroids directly inhibit phospholipase A2, blocking the formation of prostaglandins and leukotrienes and are the primary treatment of CME in many cases,
  - corticosteroids can be given orally, topically, or injected intravitreally (*off-label use*) or in the subtenonian space (*off-label use*) [3, 19].
  - adverse effects: cataracts and increased intraocular pressure.
  - diabetic patients may benefit from an intravitreal dexamethasone (0.7 mg) implant [17].

- ***Nonsteroidal anti-inflammatory drugs (NSAIDs).*** NSAIDs inhibit cyclooxygenase and can be used in the prevention and treatment of CME.
  - these are usually given topically for 3–4 months and resumed "as needed".
- ***Anti-VEGF therapy*** is superior to laser therapy alone for diabetic macular edema [21].
  - anti-VEGF therapy with bevacizumab is also indicated in the treatment of pseudophakic CME.
- Acetazolamide and methazolamide.
- ***Surgical treatment***
  - Yag laser vitreolysis in aphakic or pseudophakic eye with CME
  - peripheral laser photocoagulation
  - pars plana vitrectomy (if medical treatment is NOT effective)—especially in pseudofac [3]

The treatment of CME depends on the cause [3, 6, 9].

- ***Postoperative CME, after cataract surgery***
  - risk factors:

    anterior chamber implant
    Previous CME in the other eye
  - etiological treatment, if possible;
  - systemic carbonic anhydrase inhibitors
  - corticosteroids and topical NSAIDs.
- ***CME after other surgical procedures***—Nd:Yag laser capsulotomy, cryotherapy, laser FC
  - CME is frequently moderate, self-limiting and does not require treatment
- ***CME in retinal vascular pathology***—DR,CRVO, idiopathic retinal telangiectasias, root retinopathy, arterial macroaneurysm:
  - laser photocoagulation when indicated.
- ***CME in intraocular inflammatory pathology in: intermediate uveitis, Birdshot retinochoroiditis, multifocal choroiditis with panuveitis, Behcet's disease, scleritis***
  - inflammation control by corticosteroids and systemic immunosuppressants
  - topical corticosteroids
  - iv acetazolamide in intermediate uveitis
- ***CME induced by medical treatment***
  - adrenaline—topical
  - latanoprost—topical

  - nicotinic acid—systemic

    it is necessary to stop the medication

- ***CME in retinal dystrophies:***
  - RP
  - gyrate atrophy
  - Dominant CME

    acetazolamide might be beneficial in RP

- ***CME in vitreoretinal traction syndrome:***
  - if necessary PPV

- ***CME in the macular epiretinal membrane through the rupture of the perifoveolar capillaries***:
  - surgical excision of ERM in some cases, if there are indications.

Surgical Treatment

- PPV with posterior hyaloid peeling and meticulous attempt to reduce vitreous incarceration in the anterior segment
- ***Dominant CME***
  - 7q gene locus AD with onset between 10–20 years with progressive loss of central vision
  - Bilateral CME
  - does not respond to acetazolamide and manifests by foveolar diffusion in flower petals
  - reserved prognosis with evolution towards a possible geographic atrophy [6].

Macular Epiretinal Membrane

- They are avascular tissue proliferations of glial cells at the vitreoretinal interface that cross through fissures of the internal limiting membrane [9].
- Causes [6]
  - idiopathic
  - secondary

    previous retinal surgery is the main risk factor for MH (macular hole); photocoagulation and cryotherapy

  - high myopia

  - intraocular inflammation
  - occlusive retinal vascular disease
  - VH
  - sickle cell retinopathy
  - macular hole
  - injuries
  - intraocular tumors: angioma, hamartoma, telangiectasia, retinal arterial macroaneurysm
  - RP

- symptoms
  - ocular symptoms depend on the location and degree of membrane contraction
  - asymptomatic 80% or minimal signs in thin, transparent, non-retractable membranes
  - severe visual dysfunction (in those with RD), macro-, micropsia metamorphopsia.
  - central photopsia
  - monocular diplopia if macular pucker is present

- OCT—epiretinal membrane visible on the surface of the retina, sometimes associated with distortion of the surface of the retina
- Amsler test—abnormal.
- Clinical signs [6, 13]
  - examination in red-free light, the membranes appear transparent, translucent, or white
  - the retina can have striations, with tortuous or rectilinear vessels
  - characteristic for ERM are:

    irregular light reflex
    moderate stretch marks, vascular distortion

  - the presence of an apparent cellophane membrane across the macula, with/without vascular tractions or tortuosity, retinal striae, pseudohole, foveal ectopy, and CME
  - onset through moderate metamorphopsia, or fortuitous discovery
  - Normal or moderately low VA
  - occasionally—multiple punctate hemorrhages in the retina.

- fundus
  - grade 0—simple translucent membrane, seen as a bright light reflection of the retina (sheen like a sheet of cellophane)
  - grade 1—membranes causing retinal puckering, deforming vessels, macular pseudohole edema and macular traction (cellophane puckering)
  - grade 2—opaque, thick membranes after RD surgery with macular retinal edema, retinal wrinkling.

- Complications
  - ectopy of the fovea
  - tractional detachment of the macula
  - CME
  - intra-/preretinal hemorrhages
- prognosis
  - stable disease in 75%
  - after surgical treatment in 60–85% VA improves by at least two Snellen lines
  - unfavorable prognosis

    adjacent macular pathology
    Low preoperative VA
    prolonged evolution before surgical treatment

Treatment

- Ablation of the membranes by surgical treatment by PPV with peeling of the ILM after staining (indocyanine green, brilliant blue) in patients with decreased VA
- PPV with membrane peeling
  - can improve VA
  - reduce metamorphopsia
- Postoperative complications after PPV
  - cataract 70% at 2 years
  - retinal tears and RRD (rhegmatogenous retinal detachment)
  - VA decrease (15%)
  - relapse (5%)

Epimacular Membrane

The epimacular membrane develops on the surface of the macular retina primitively (idiopathic) or secondarily in other eye diseases—RVO, retinal tears, VH, diabetes, intravitreal surgery Gass classifies the epimacular membrane in 3 grades [7, 8]:

- grade 0—**cellophane maculopathy** translucent membrane (resembles cellophane) on the surface of the macula, without distortion of the macular region.
- grade 1—**wrinkled cellophane maculopathy**—in which the membrane exerts tangential traction on the macular retina
- grade 2**—macular pucker**—thick, sometimes retracted, opaque membrane covering the vessels, pulling on the retina
  - onset with metamorphopsia, decreased VA, distorted perception of objects

  - bilateral condition in 25%, epimacular membrane, in time it can be complicated with macular edema and RPE rearrangement indicating reserved surgical prognosis

Complementary Exams
- Amsler test reveals metamorphopsia
- OCT
  - highlights the hyperreflective epiretinal membrane, macular edema, vitreoretinal tractions
  - represents the reference examination in postoperative follow-up
- FA—not routinely indicated
- Surgical treatment by PPV and membrane dissection associated with peeling of the internal limited membrane

Fundus
- Retinal folds and whitish striae
- Important vascular tortuosity

Treatment—PPV with membrane peel (reduce metamorphopsia and improve vision)

Macular Pucker—Macular Fold [6, 7]

- It is a thick and contracted membrane that retracts and requires treatment.
- Symptoms—metamorphopsia, decreased VA.
- Fundus—retinal folds, white striae, vascular tortuosity.
- Treatment—ablation of the membranes by vitrectomy.
- Complications
  - intraoperative: retinal hemorrhages, retinal tears;
  - postoperative: cataract, possible RD after a new tear pulling the retina 3–5% in the lower 1/2 of the retina.
- Vitreoretinal proliferation where the membranes are stretched over a detached retina
  - It is the main cause of failure in RD surgery because it allows the formation of retractable membranes.

Choroidal Folds

- There are folds of the internal choroid, Bruch's membrane, RPE and sometimes the sensory retina, produced by choroidal congestion, scleral folds with contraction of the Bruch's membrane.

- Etiologically they are:
  - idiopathic associated with hypermetropia
  - choroidal tumor
  - prolonged ocular hypotony
  - chronic papillary edema
  - posterior scleritis
  - scleral indentation
  - orbital disease
- Symptoms—Normal or decreased VA depending on location.
- Ophthalmoscopic—horizontal parallel folds with one pale and one dark ridge.
- FA—alternation hyper—with hypofluorescence.

Idiopathic Polypoid Choroidal Vasculopathy

- They are hemorrhagic episodes due to aneurysmal dilatations (polyps) at the level of the internal choroidal vessels.
- Symptoms—slow, unilateral decrease in VA.
- Fundus—serosanguineous PED.
- Treatment—LASER photocoagulation if the fovea is threatened.

Maculopathy and Congenital Coloboma of the Papilla

- A severe macular detachment occurs due to subretinal fluid probably of vitreous or subarachnoid origin.
- Onset at puberty with metamorphopsia.
- Fundus—superior papillary coloboma and oval macular serous detachment with small precipitates on the posterior face.
- Treatment
  - Follow-up
  - argon LASER photocoagulation of the temporal border of the papilla, with VA improvement
  - vitrectomy $\pm$ photocoagulation.

Toxic Maculopathy [9, 10]

Antimalarials

- *Chloroquine*
  - it is used in the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, SLE, malaria prophylaxis;
  - the drug is eliminated slowly and accumulates in melanin-containing structures (RPE, choroid);
  - symptoms

    transient accommodation difficulties
    central/paracentral scotoma, absolute scotoma 4–9%
    decreased vision
    visual field constriction
    night blindness
    photopsia
    dyschromatopsia
    photophobia
    decreased color vision.

- Fundus
  - decreased foveal reflex
  - reversible macular pigmentation
  - irreversible bull's-eye maculopathy
  - bone-spicule, pale disc, as in RP
  - decreased vascular caliber
  - cornea verticillata (subepithelial corneal deposits)
  - poliosis

Hydroxychloroquine—Plaquenil

- If the dose does not exceed 400 mg/day, it's a very small risk of retinal toxicity

Phenothiazines

- *Thioridazine—Melleril*
  - it is used in the treatment of schizophrenia and psychoses

  - daily dose 150–600 mg, retinal toxicity may occur at a dose of 800 mg for several weeks
  - Fundus—plaque pigmentation and RPE atrophy.

- *Chlorpromazine—Largactil*
  - used for sedation and in schizophrenia
  - daily dose 75–300 mg, retinotoxicity occurs at doses higher than 300 mg/day for several months
  - Fundus—non-specific pigmented granulations
  - Other effects—yellow/brown deposits on the corneal endothelium, lens capsule.

Deferoxamine (Desferal)

- It is an iron and aluminum chelator and may be present in patients who have received multiple transfusions.
- Toxicity is manifested by: decreased vision, nyctalopia, visual field changes
  - gray macula with perimacular and diffuse generalized pigmentary changes, which may persist even after discontinuation of treatment, sometimes bull's-eye maculopathy
- Toxicity is reduced if the drug is administered intermittently or discontinued.

Interferon α

- It produces vascular occlusions, probably through deposits of immune complexes.
- Toxicity is manifested by: cotton wool spots, intraretinal hemorrhages, CME, rarely vascular occlusions.

Quinine

- Toxicity occurs at the level of the neurosensory retina and is manifested by: blurred vision; decreased visual field; photophobia, *single dose greater than 4g can cause permanent blindness!*
- Fundus: venous engorgement, red/cherry spot, decreased retinal vascular caliber, optic atrophy, vascular occlusions.

Topiramate

- It is a drug used in the treatment of epilepsy, migraine prophylaxis, in the treatment of bipolar disorders and as a second-line treatment in idiopathic ICP in patients intolerant to acetazolamide.
- It can produce:
  - myopia
  - angle closure glaucoma
  - retinal striae that produce vitreomacular traction
  - uveal effusion syndrome with lens subluxations.

Drug-induced Crystalline Maculopathies

- *Tamoxifen—Nolvadex*
  - used in breast cancer
  - daily dose 20–40 mg, toxicity occurs at higher doses, several months
  - Fundus—yellowish macular deposits with a crystalline appearance, CME
  - Other effects:

    cornea verticillata
    optic neuritis
- *Canthaxanthin*
  - used for tanning
  - retinotoxicity appears in prolonged use in the form of small, refractive, yellowish deposits located in the posterior pole.
- *Methoxyflurane—Pentran*
  - anesthetic gas with crystalline retinal toxicity of retinal vessels, without clinical consequences.

Traumatic Maculopathy [18]

- *Post-contusion*

Berlin Edema

- Fundus

  - red foveola
  - edema and perifoveolar stellate retinal folds
  - fine perifoveolar hemorrhages, along the vessels
  - gray tinge of posterior pole.
- Evolution
  - resorption of macular edema with loss of foveolar reflex
  - unfavorable in 25–40%

    lamellar hole 1/4–1 PD, dark red with whitish dots
    pigmentary and atrophic remodeling of the macular region
- Treatment: antispasmodics, vasodilators, do NOT influence the course of the disease.

Choroidal Tears

- located concentrically to the papilla, rarely perimacular
- single, multiple, accompanied by hemorrhages and edema
- they can be complicated with CNV, serous or hemorrhagic RD
- treatment
  - LASER photocoagulation
  - vitrectomy within the first 10 days (if indicated) to prevent subretinal fibrosis.

Traumatic Macular Hole

- Post-contusion necrosis may be followed by macular edema, macular cyst, in which rupture of the inner layer of the cyst (luni) may occur and produce **lamellar hole** or full-thickness tear with **macular hole.**
- Treatment
  - Follow-up
  - vitrectomy if needed.

Purcher Retinopathy

- It is caused by trauma to the chest, head, long bones
- Uni-, bilateral is accompanied by important decrease of VA with central scotoma and DPA.
- fundus

  - generalized retinal edema secondary to ischemia (whitish appearance of the retina)
  - large exudates
  - hemorrhages along the vessels
  - papillary edema.

Valsalva Retinopathy

- It is produced by the sudden and severe increase in intrathoracic, intra-abdominal pressure, which causes retinal hemorrhages.
- Uni-, bilateral small preretinal macular hemorrhages, which may resorb after a few months, or require vitrectomy.

Terson Syndrome

- Vitreous and intracranial hemorrhages

Abused Newborn Syndrome

- Ocular
  - pre-, intra-, subretinal hemorrhages
  - exudates
  - papillary edema.

Solar Maculopathy

- It sets in 4–6 h after sun exposure with uni-, bilateral decrease of central VA and metamorphopsia, central scotoma.
- Fundus—small yellowish spots with gray edges at the level of the foveola.
- Improvement after 4–6 months.

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Chapter 17
Age-Related Macular Degeneration (AMD)

H. T. Stanca

Abstract The Age-Related Macular Degeneration (AMD) is one of the most important etiology of elderly people's blindness in developed countries. Classicaly there were descibed two AMD types: a dry and a wet form, but the newest classifications consider an early (and intermediate) stage correlated with drusen in diferent sizes and/or pigmentary anomalies and a late stage also, divided in two different fenotypes: geographic atrophy and macular exudation going on a disciform scar. The macula involvement obviously induces a central vision loss with a progressive deterioration of the quality of life for the patients involved. Besides clinical examination with the slit-lamp and special lenses, there are several diagnostic techniques (optical coherence tomography, angiography by optical coherence tomography, fluoresceine angiography, indocyanine green angiography, fundus autofluorescence, retromode imaging) included in the general term of multimodal investigations. Historically the AMD treatment consisted in laser photocoagulation, radiotherapy, subretinal surgery, retinal pigment epithelium transpantation, transpupillary thermotherapy, photodynamic therapy, but nowadays the mainstay is the antiangiogenic therapy with antiVEGF agents. Since 2005 there have been used bevacizumab, ranibizumab, aflibercept, brolucizumab, faricimab with excellent results, but all of these had adressed only the wet AMD types. New classes of complement inhibitors were created to slow or to stop the progression of geographic atrophy in its insidious way to the fovea, but this dry AMD treatment is still under evaluation. The genetic treatments with different kind of viral vectors sound extremely promising and quite soon We'll have new solutions for this debilitating disease.

Keywords Age related Macular Degeneration · Exudative form macular syndrome · Subretinal endolaser · Macular translocation · Non-exudative form

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macular degeneration · Age-Related Macular Degeneration (AMD) · Elderly blindness · Dry AMD · Wet AMD · Early stage AMD · Intermediate stage AMD · Late stage AMD

Age-related macular degeneration is the main cause of severe visual impairment in the population over 60 years old in industrialized countries [1].

The prevalence of macular degeneration in the 40–49-year-old population is 2.1%, increasing dramatically to 35% in the over 80-year-old population [2]. Incidence continues to increase both as a result of increased life expectancy and improved management of other eye conditions.

There are two stages of macular degeneration: early and late.

- in the early stage, the formation of large drusen and pigmentary abnormalities are characteristic.
- in the late stage, two forms are distinguished: dry AMD and wet AMD.

The dry or non-exudative form is characterized by:

- atrophic changes of the macula, presenting a slow deterioration and a better visual prognosis than the wet, exudative or neovascular form.
- the progressive disappearance of the retinal pigment epithelium (RPE) causes the appearance of focal areas of atrophy that expand slowly and may fuse.
- the affected areas have no visual function because the loss of RPE is associated with the degradation of photoreceptors (Gass called this aspect "geographical atrophy of the RPE", being the final form of manifestation of AMD in the absence of clinical evidence of the association of choroidal neovascularization).
- The non-exudative form of AMD is a lot more frequent than the exudative one. Its representative elements are:
  - present drusen
  - changes at the RPE level and atrophy.
  - absence of hemorrhages, hard subretinal exudates or subretinal fluid

The exudative form of age-related macular degeneration:

- severe deterioration of central vision occurs with predilection as a result of the formation of pathological choroidal neovessels, which structurally and functionally modify the macular region.
- choroidal neovascular membranes (CNVM) are characteristic elements, but are associated with many other conditions [3]:
  - AMD
  - ocular pseudohistoplasmosis
  - other inflammatory conditions
  - myopic macular degeneration

– injuries
– retinal dystrophies
– angioid striae.

CNV in the advanced stages of AMD can cause irreversible loss of central vision to the level of "legal blindness". This type of visual disability, in which there is still a residual peripheral visual field, considerably reduces the adaptation of the individual to the environment, making it impossible to read, drive, recognize the facial features of the people around, thus altering the quality of life and the autonomy of the affected people.

From a physiopathological point of view, there are several theories that have tried to identify the cause and the way of triggering in the case of the above-mentioned pathological changes, but none of them is infallible. Classically, four theories are stated: traditional or senescence, issued by Young and Eagle [RPE senescence can lead to the fragmentation of Bruch's membrane, with the release of macrophages and matrix metalloproteinases (MMPs), which break the antiangiogenic barrier and cause the release of angiogenic factors (VEGF/TGF-ß/PDGF/bFGF)]; vascular, issued by Friedman, which specifies that when the choroidal vascular resistance is greater than the cerebral vascular resistance, drusen appears, and when the inequality reverses, choroidal neovascularization occurs; the oxidative stress theory, based on the toxic involvement of free radicals, and the genetic theory, which captures the predisposing role of components such as the ABCA gene. To all of them is added the proactive effect of inflammation, which is found in many stages of the pathogenic process.

Wet AMD is characterized by the presence in the subretinal space of liquid and/or hemorrhages and/or hard exudates.

Exudative AMD is accompanied by detachment and rupture of the RPE with the development of choroidal neovascularization (CNV).

Several histo-clinical entities are distinguished within this pathological context:

Retinal Pigment Epithelial Detachment-PED

- It is a frequent manifestation of AMD, produced by the accumulation of lipids in Bruch's membrane, which makes it strongly hydrophobic, thus blocking the flow of ions and fluids from the cells of the retinal pigment epithelium. It is clinically characterized by a well-defined RPE elevation, which can be associated with hemorrhages and/or lipid exudation. Sometimes a detachment of the overlying neurosensory retina is also observed. There are two forms of PED: serous and fibrovascular [4].

RPE Rupture

- it starts suddenly with a decrease in central vision; it is observed ophthalmoscopically as a dehiscence through rupture of the RPE in the shape of a crescent with free, folded edges and retractions located at the level of the RPE; in the FA examination, hypofluorescence is noted under the free edge with progressive adjacent hyperfluorescence; the prognosis is reserved in the retrofoveolar location.

Choroidal Neovascularization-CNV

- CNV is born by the proliferation of choriocapillaries that cross Bruch's membrane; choroidal neovessels are "new", abnormal blood vessels, originating in the choroid, which penetrate Bruch's membrane, spread under the retinal pigment epithelium, respectively the neurosensory retina, and irreversibly influence central vision through: edema, exudation, hemorrhages; the appearance and development of neovascular choroidal membranes induces the deterioration of central visual acuity, through the destruction and dysfunction of the photoreceptors in the macula region; CNV can precede or follow PED, not being a direct relationship between them.

Retinal Angiomatous Proliferation (RAP)

- It is a particular form of CNV associated with retinal capillary proliferation and telangiectatic response; the prevalence of RAP in neovascular AMD is 10–15% [5]; It occurs more frequently in older patients and has a marked tendency of bilateral and symmetrical involvement of the neovascular component; there is a certain predilection for women and Caucasians, an element of differentiation from polypoid CNV that occurs in pigmented races.

Clinical Evaluation in AMD

Macular syndrome: can be defined as a set of symptoms, associated with changes in central vision, respectively signs of macro- or microscopic changes in the structure of the macula, which occur in a clinical picture defined by alteration of central vision, and which correspond to various causes.

- symptoms:
  - **alteration of central vision**—represents the major symptom of macular pathology; the patient reports an obstacle ("a spot") of central vision (positive scotoma), in contrast to the negative scotoma from optic nerve lesions perceived as a "hole" in the center of the visual field [6].
  - metamorphopsia—it is a change in the shape of the perceived image (a deformation of it); it is specific to macular diseases; does not occur in optic nerve damage.
  - micropsia represents the decrease in image size, due to the lateral displacement of the foveal cones; it is not very common.
  - macropsia—involves the increased perception of the size of the images and appears through the agglomeration of the foveal cones; it is very rare.
  - change in color vision—appears mostly in the blue-yellow axis, but it is not a specific feature of macular lesions and often appears late.

Methods of examining structural changes (signs) of the macula they are represented by:

- Biomicroscopy of the fundus
  - it is the first step in the diagnosis of AMD, but also of other macular diseases. The stereoscopic image provided by the biomicroscope and filtered through specific lenses provides fine details about macular structural changes. Non-contact lenses of 78 D and 90 D are routinely used but contact lenses of the "area centralis" type, "super-macula" etc. would still be preferable, for superior visualization.
  - The dry (non-neovascular) form of AMD is characterized by the presence of drusen, pigmentary changes and, in advanced forms, geographic atrophy. Drusen (soft drusen) appear as yellow deposits ($\geq$ 63 microns), between the RPE and Bruch's membrane (BM). Pigmentation changes occur in RPE and can have a hypo- or hyperpigmented appearance. Geographic atrophy appears as a round or oval, well-defined area of hypopigmentation, representing RPE and choriocapillaris atrophy.
  - The wet (neovascular) form of AMD is characterized by the appearance of choroidal neovascularization (CNV). CNV appears as a deep gray-green tissue prominence in the retina (actually subretinal) and may be associated with subretinal hemorrhages, lipid exudation, neurosensory retinal detachment, or RPE detachment.
- Fundus autofluorescence
  - Excess accumulation of lipofuscin in the RPE, documented by imaging as focal areas of increased autofluorescence, has been proposed as a marker for RPE disorders and photoreceptor degeneration. Structures that can absorb light, prior to RPE, such as blood vessels and macular pigment, as well as the lack of autofluorescent material in RPE atrophy, induce a decrease in the autofluorescent signal of the fundus. Focal reduction of autofluorescence especially over large areas in the macula is suggestive of geographic atrophy, the most severe form of dry AMD.
  - Autofluorescence images of choroidal neovascularization present a characteristic reticular appearance.
- Fluorescein angiography (FA)
  - Geographic atrophy is identified in the early stages of FA as a well-defined area of "window defect" of the RPE within the area of clinically evident atrophy. Late phases of FA show persistence of dye in the choroidal circulation, seen through the window defect, but no leakage (diffusion or extravasation).
  - In the case of neovascular AMD, FA allows the CNV to be highlighted, the type of neovascular membranes present—classic or occult, their edges (well or poorly demarcated), their composition (predominantly classic, minimally classic or occult without classic) and localization (extrafoveal, juxtafoveal, respectively subfoveal).
  - The angiofluorographic signs of CNV are early hyperfluorescence of neovessels (in the depth of the retina); diffusion or "leakage" during the fluorescein

transit; the progressive increase in size and intensity of the "leakage"; the late "pooling" of the dye in the sub-RPE or sub-retinal space.

- Indocyanine green angiography (ICGA)
  - is useful in highlighting occult CNV. These appear as ill-defined areas of "stained" hyperfluorescence on FA, but the same occult lesions appear as well-defined hyperfluorescent plaques or "hot spots" on ICGA.
- Optical coherence tomography (OCT)
  - Choroidal neovascular membranes have varied appearances on OCT. There are direct and indirect OCT signs of the presence of choroidal neovascularization (CNV). Indirect signs are retinal thickening assessed quantitatively by retinal mapping (due to intraretinal cysts, macular edema or subretinal fluid accumulation); the elevation of the neurosensory retina with the disappearance of the foveal depression; the prominence of the highly reflective posterior band associated with the RPE take off. Direct signs refer to the OCT appearance of the shapes defined by CNV. Thus, the classic forms can appear as an intensely reflective fusiform thickening, between the retina and the external hyperreflective band, which corresponds to the RPE/Bruch's membrane/choroid complex. Occult forms may appear as prominences of the RPE or as irregularities of the hyperreflective outer band.
  - In geographic atrophy from non-neovascular AMD, OCT can reveal increased light signal intensity from the posterior portion of the choroid, as the atrophied RPE allows deeper light penetration.
  - Fibrovascular detachment of the RPE is identified as a well-defined prominence of the reflective band of the RPE above a moderately reflective band.
  - Among the multiple possibilities, OCT has offered ophthalmologists two special values: the ability to make sections through the retina and the function of quantifying retinal morphological changes [7].
  - OCT provides additional information compared to other diagnostic methods and is required as a confirmation and monitoring test of atrophic and neovascular AMD, both pre- and post-treatment.
- Optical coherence tomography angiography (OCT-A)
  - OCT-A has developed more recently using extremely high acquisition speed OCT systems. It is a technique imaging that offers the possibility to identify the 3D structures of the retinal and choroidal blood network, layer by layer, through a non-invasive investigation.
  - OCT-A detects changes in light scattering between a series of scans taken in rapid succession.
  - In a static eye, the only changing structures are the red blood cells moving through the large blood vessels and capillaries.
  - High reflectivity implies the mobility of red blood cells, and low reflectivity implies their absence.

- It is obtained by identifying the subtle differences between repeated type B scans, taken in exactly the same position and for exactly the same tissue.
- The differences between the images are thought to be due to blood movement.
- The advantage of OCT-A is that the vascular resolution is usually superior to that provided by FA and does not involve invasive maneuvers – injection of contrast substances.
- The limits of this investigation are represented by the fact that the interpretation depends on movement, no contrast substance being used,so it does not have the same sensitivity to leakage such as FA [8].

AMD Treatment

Over the past twenty years, enormous efforts have been focused on finding an effective treatment for AMD, both its dry and wet forms. Since exudative AMD is the most aggressive form and with the most severe visual disabling potential, it has been a favorite target for therapeutic trials.

Dry AMD, which involves tissue atrophy, has been approached from a therapeutic point of view, especially through methods of prophylaxis or slowing down the evolution of the condition, but also through attempts to replace the missing tissue (RPE and photoreceptors) through electronic prostheses or cell transplantation [5].

The treatment methods used were diverse:

- laser photocoagulation
- radiotherapy
- surgical treatment
- artificial vision
- transpupillary thermotherapy
- photodynamic therapy
- pharmacotherapy
- combined therapies
- gene therapy

Laser Photocoagulation

- Photocoagulation aims to obliterate the abnormal blood vessels and limit the damage in the macular region, the exact location of the CNVM being mandatory; **the indication of choice is classic juxtafoveal and extrafoveal CNVM;** currently, laser photocoagulation is only a backup solution, in the absence of other more effective methods [8].
- Extrafoveolar choroidal neovascularization, defined as well-demarcated CNV located between 200 μm and 2500 μm from the center of the foveal avascular zone (FAZ), can be treated with or without retrobulbar anesthesia; the neovascu-

lar complex is treat in a way confluence to produce bleaching uniform of the retina; Treatment the lesion extends 100 μm beyond the edges, using a green argon laser with a spot of 200–500 μm, with a duration of 0.1–0.5 s.

- Juxtafoveal neovascularization is defined as well- demarcated CNV located from 1 μm to 199 μm from the center of foveal avascular zone (FAZ); the neovascular complex is treated in a confluent manner to produce uniform retinal whitening; it is recommended to treat 100 μm beyond the edges of the lesion, except for the foveal area, where the treatment beyond the edges of the lesion is dependent on the distance between the hyperfluorescent area and the center of the FAZ.

Radiotherapy

- Cumulative doses (multiple fractions) of up to 25 Gy do not damage the retina or the optic nerve; irradiation of the macula in the case of occult or classic CNVM inhibits angiogenesis either directly (destruction of neovascular endothelial cells and cytokine-producing macrophages), or indirectly (by affecting regulatory genes in the cells, which produce regulatory cytokines of vascular endothelial growth factors) [9]; currently the NeoVista system is available, a device (intraocular applicator made of Strontium-90) that places the radiation source in the immediate vicinity of the CNVM, through an intravitreal approach, allowing the irradiation of an extremely precisely delimited area, respectively of a reduced retinal volume; the association with the injection of antiVEGF agents led to spectacular results (Cabernet study); by treating a small area of the retina with a therapeutic dose of 24 Gy, and by administering clinically significant levels of radiation to a small retinal volume, the risk of radiation retinopathy is greatly reduced or even eliminated, compared to the old therapeutic methods that used ionizing radiation.

Surgical Treatment

- multiple surgical approaches have been tried [6], namely:
  - direct extraction of CNVM
  - macular translocation (limited or complete)
  - subretinal endolaser surgery (PEELS)
  - RPE transplantation, respectively photoreceptors
  - autologous RPE-choroidal patch transplantation
  - epi- or subretinal microphotodiode implant

Direct Extraction of CNVM

- CNVM located subretinally (under the neurosensory retina and above RPE as much as possible) have the best prognosis, since the preservation of the RPE is crucial in restoring visual function; the operative technique involves posterior

vitrectomy, detachment of the neurosensory retina overlying the membrane, dissection and extraction of the subretinal membrane, hemostasis, fluid-air exchange; Currently, the method has **limited indications** and is especially applied to **extrafoveal, peripapillary and juxtafoveal CNVM** [6, 7].

Macular Translocation

- represents the displacement of the fovea on a healthy RPE; two types are identified—complete and limited

Full Macular Translocation

- involves complex surgical maneuvers; operative times involve the extraction of the lens by phacoemulsification and the implantation of a posterior chamber intraocular lens; posterior vitrectomy; total retinal detachment; 360° peripheral retinotomy; folding the retina, usually nasally, highlighting the CNVM and removing it and associated bleeding; rotation of the retina clockwise or trigonometrically, (the rotation can be between 30° and 60°)—as a rule, the alignment of the fovea on the site of the former temporal-superior arch is preferred; reattachment of the retina with perfluorocarbon liquid; extensive photocoagulation of the retinal periphery (after placing the retina on an area with healthy RPE and after spreading it); internal tamponade with silicone oil; silicone oil extrusion and extraocular muscle surgery to correct excyclotorsion at a variable interval, between 3 and 6 months [7].

The limits of this technique are given by the difficulty of the maneuvers, by the fact that it is difficult to reproduce and presents serious and frequent complications.

Limited Macular Translocation

- involves "sliding" the fovea on an area of healthy RPE, without 360° retinotomy; it is carried out by two methods—scleral shortening, respectively scleral imbrication

Translocation by scleral shortening (internal) ("scleral infolding") consists in the dissection of a semilunar flap in ¾ of the thickness of the sclera, at the level of the equator, in the supero-temporal or infero-temporal quadrant; vitrectomy through pars plana; retinal hydrodissection to create retinal detachment; suture of the scleral defect, with the consequent shortening of the wall of the eyeball and the "slipping" of the fovea on an area with healthy RPE; fluid-air exchange and gas injection with retinal reapplication. Supero-temporal scleral shortening produces inferonasal fovea translocation, and infero-temporal shortening causes superonasal

translocation. CNVM, which has become extrafoveal, is treated by laser photocoagulation postoperatively [7].

Translocation by scleral imbrication ("external scleral shortening—"scleral outfolding") consists of applying 3-4 sutures with non-absorbable 5"0" threads, between the superior and external rectus muscles, located 2 mm posterior to the rectus insertion, with a width of 4.5–6 mm; vitrectomy through pars plana; detachment of the retina with a 40 Ga cannula (hydrodissection with BSS); two posterior retinotomies in the inferior temporal and inferior nasal quadrants (at approximately 180° from each other); fluid-air exchange, without subretinal fluid drainage; sitting position postoperatively, for moving the inferonasal fovea [7].

Of the two limited translocation techniques, the one with scleral imbrication and retinotomy allows greater translocation and is of choice in larger CNVM or in large-area RPE atrophy, and the scleral shortening is of choice in smaller CNVM (from degenerations myopic) [5, 7].

Macular translocation surgery has demonstrated the possibility of ameliorating VA in certain patients, but the potential complications remain significant.

Subretinal Endolaser Surgery (PEELS)

- "Pigment epithelium endoscopic laser surgery (PEELS)" is a technique that involves: vitrectomy through the pars plana; iatrogenic detachment of the retina in the posterior pole; insertion of the subretinal laser endoscope through a single transretinal hole; subretinal endoscopic photocoagulation of the CNVM-RPE complex; immediate intraoperative reattachment of the retina through fluid-air exchange; it is an expensive technique due to equipment and with inconstant results, as such it is used extremely rarely nowadays [9].

Transplantation of Pigment Epithelium/Photoreceptors

Transplantation of RPE [5] can be done in several forms:

- tissue—harvested from an intact area and implanted at the same time by the operator on the excision area of the CNVM.
- fresh cells – scraped from an intact area and disseminated on the surface of the damaged RPE.
- cultured cells – RPE cells or iris pigment epithelium (IPE) from the same individual (autograft); from another individual, HLA phenotypes (allograft);
- human fetal retinal cells (stem cells); fetal porcine retinal cells (xenograft).

The objectives of the transplant are:

- replacing dead or diseased RPE cells.

- Bruch's membrane repair.
- repopulation of photoreceptors.
- prevention of cell degeneration due to disease recurrence.

The difficulties of cell transplantation are related to the identification of the ideal source for transplantation; the efficiency of initial attachment and proliferation of cells seeded on Bruch's membrane; ensuring a sufficient number of cells; of rejection prevention.

- ***Heterologous stem cell transplantation***
  - The causes of the failure of this intervention are rejection of the graft; failure to attach to Bruch's membrane; the impossibility of obtaining a constant cellular monolayer; destruction of transplanted cells; loss of RPE cell polarity; loss of cell differentiation characteristics.
- ***Transplantation of RPE HLA phenotyped cells***
  - It is an experimental technique, under development, addressed exclusively to cases of non-neovascular AMD (atrophic forms).
- ***Transplantation of cells from the Irian Pigment Epithelium***
  - It represents an autotransplantation of cultured and cryopreserved IPE cells, which are then implanted in the form of a suspension on ultrathin type I collagen sheets; the success of this transplant depends on: ensuring a sufficient number of cells; the ability of IPE cells to form a monolayer, covering the exposed segments of the photoreceptors; of acquiring the differentiating characteristics of RPE.
- ***Autologous RPE cell transplantation***
  - Patch-type integral transplantation of autologous RPE—Bruch's membrane—choroid, harvested either from areas located in the vicinity of the excised membrane or from the medial periphery, is a technique already frequently used for the treatment of both wet and dry AMD.
  - For exudative AMD, the transplantation of RPE cells in suspension, freshly harvested from the subretinal area, has been proposed as a less traumatic technique.
- The future of retinal transplantation depends on improving the techniques of harvesting, cultivating, and preserving cells; prolonging the survival of cell transplants; the control of the long-term immune response and the possibility of obtaining and maintaining transplanted cells in monolayer.
- ***Autologous RPE and choroidal patch transplantation***
  - The latest surgical technique in neovascular AMD refers to the transplantation of a patch of retinal pigment epithelium, Bruch's membrane, choriocapillary, and choroid (RPE-FTAP; "retinal pigment epithelium—full thickness autologous patch") .

- The argument for transplanting an FTAP from the periphery to the central region refers to the supporting potential of these cells towards foveolar photoreceptors. Also, the maintenance of the retinal pigment epithelium grafted in a monolayer by Bruch's membrane and the underlying choroid led to its viability and the realization at the site of the new positioning of both the supporting role for photoreceptors and the secreting role of antiangiogenic factors (pigment epithelium derived factor), for antioxidant protection and inhibition of potentially recurrent choroidal neovascularization.
- The patch is harvested in the entire thickness of the internal wall, from the temporal periphery of the retina. This, however, obviously involves performing a thorough posterior and extreme peripheral vitrectomy, iatrogenic detachment of the temporal retina by injecting fluid into the subretinal space, performing a retinotomy in the temporal periphery of 180–200 ^{0}, °removing the subfoveolar neovascular membrane, delimiting the graft by diathermy in the middle periphery of the uvea, harvesting the patch and transpositioning it centrally, above the foveola, reattaching the retina and stabilizing it by laser photocoagulation and internal tamponade with silicone oil.
- The success of the intervention is determined by several milestones that need to be followed: decentering of the patch can lead to its atrophy under the fovea; the edges of the patch should not be touched during manipulation because RPE damage leads to its atrophy; the harvesting site of the graft must be far from the place of final destination due to the risk of proliferation of a fibrotic scar from the harvesting site, which could alter the graft; avoiding intra- and postoperative bleeding through an extensive diathermy both for the cauterization of the source vessels of the excised choroidal neovascular membrane and at the edges of the graft harvesting area. Visual prognosis appears to be determined by identification of the outer nuclear layer and photoreceptors on preoperative optical coherence tomography scans.
- Pertile et al. report on a series of thirteen eyes, followed up to 20 months postoperatively, the reperfusion of the grafted choroidal bed, identifiable as early as one week postoperatively, the absence of intra- and postoperative complications. Patients were followed up by complete ophthalmological examination, angiography (FA), indocyanine green angiography (ICGA) and optical coherence tomography (OCT) [10].
- However, it should be noted that this technique is difficult to perform and is not without potential complications (proliferative vitreoretinopathy, retinal detachment, vitreous hemorrhage, subchoroidal hemorrhage, graft atrophy). Careful selection of patients and correct execution of all operating times are essential for therapeutic success.

Artificial Vision

- it involves taking images by a video camera, transforming them into an electrical signal, encoding the signal and then sending it by telemetry to a receiver implanted in the occipital region; the receiver will decode the signal and generate a type of current pulses specific to the stimulus and addressed to the visual cortex [5].

Cortical Prostheses

- The first attempts in the area of artificial vision had as a target the stimulation of the visual cortex; the cortical implant models most used in current experiments are the Ilinois intracortical visual prosthesis and the Utah electrode set.

Optic Nerve Prostheses

- The optic nerve has also been evaluated as a seat for visual prostheses; however, the axonal density at the level of the optic nerve creates difficulties in obtaining focal neural stimulation and in the perception mechanism.

Retinal Prostheses

- There are epiretinal implants, in which the device is implanted in front of the retina after posterior vitrectomy (the electrical stimulation in this technique initially meets the inner retina) and subretinal implants, in the space between the neurosensory retina and the RPE; this space can be accessed either through retinotomy or through a sclero-choroidal pocket.

A great progress has been made in the field of artificial vision, but the presence of devices available on the market is still awaited.

Transpupillary Thermotherapy (TTT)

- It is a technique based on hyperthermia, which involves the progressive heating of the subfoveal CNV with the help of the diode laser, in order to determine the occlusion of the neovessels [6, 7]; infrared wavelength (810 nm) penetrates the retina and RPE and affects especially the CNVM, with a minimal thermal effect on the outer retina; the treatment is done with a single large spot, which covers the entire choroidal neovascular complex. An increased efficiency of this technique compared to laser photocoagulation for occult CNVM was found.
- There are three levels of hyperthermia:
  - between 42–44 ° C there is no destructive effect on cells and potentiates the effect of radiotherapy on choroidal melanomas.
  - between 45–60 ° C tumor necrosis occurs without the need for concurrent radiotherapy.
  - above 60 ° C, coagulation necrosis occurs.

- TTT is useful in VA stabilization in occult or minimally classic CNVM and is preferred for conversion of occult membranes to classic membranes and in the treatment of recurrent subfoveal CNVM.
- TTT has also been shown to be useful in the management of intraocular tumors, including retinoblastoma or malignant choroidal melanoma.
- The combination of TTT with photodynamic therapy (PDT) can be effective.
- TTT is maintained as an alternative therapeutic option, in well-defined situations

Photodynamic Therapy (PDT)

- It is a technique that achieves selective thrombosis of the target tissue and involves isolated vascular occlusion through a photochemical reaction, without collateral thermal damage and with the maintenance of choriocapillary perfusion; PDT is based on the property of light absorption by a photosensitizing agent, with its consequent activation [7].

Verteporfin photodynamic therapy (PDT) has been used for the treatment of predominantly classic subfoveal choroidal neovascular membranes in AMD; subfoveal choroid neovascular membranes secondary to histoplasmosis; subfoveal choroidal neovascular membranes secondary to pathological myopia [6, 9].

- PDT consists of 2 stages:
  - intravenous administration of the photosensitizing drug, which localizes to cells with a high rate of proliferation, such as those in choroidal neovascular membranes or tumors
  - local activation of the drug with a laser of a specific, nonthermal wavelength

The laser does not heat or photocoagulate the tissues, instead, its energy produces a photochemical reaction and moves the drug into a higher energy state; the drug thus activated releases the energy of neighboring oxygen molecules, leading to the formation of reactive oxygen species and free radicals. This process leads to endothelial cell damage, platelet adhesion, vascular thrombosis and capillary closure.

Mild adverse reactions to this drug have been described, mainly related to photosensitivity and patient avoidance of sun exposure for a week, some mild allergic reactions, sometimes back pain, as well as severe decrease in VA in 1–4% of cases

The main indication of PDT is classic subfoveal CNVM, occult CNVM with signs of evolution or recent progression, as well as CNVM from degenerative myopia. PDT reduces vision loss, reduces progression of leakage from CVN, reduces CNVM growth and stabilizes contrast sensitivity [7].

The limits of this method are given by the rather high rate of relapses (30% after 3 months), the need for retreatment and the very high costs of the active substance [9].

Drug Therapy

- the principles of this therapy are based on the use of substances that:
  - block local or general inflammation
  - blocks free radicals
  - inhibits the release of vasoforming factors, stimuli of choroidal or retinal neovascularization.

Corticosteroids

- The corticosteroids used are triamcinolone, fluocinolone, dexamethasone and anecortave acetate.
- Corticosteroids have the effect of:
  - stabilization of the hemato-retinal barrier.
  - resorption of exudates.
  - blocking inflammation.
  - blocking angiogenesis by inhibiting leukocytes (macrophages) that release angiogenic factors [6].
- Mode of administration
  - intravitreal implants—Fluocinolone acetonide (Retisert), Dexamethasone (Porsudex, Ozurdex); they have a medium and long-term effect—from 6 months to 2–3 years
  - intravitreal injections – Triamcinolone acetonide (Kenalog, Kenacort, Triamhexaal, Vitreal S), Dexamethasone; short- and medium-term effect—from 1 to 3–6 months
  - parabulbar or subtenon injections – Anecortave acetate (Retaan)
  - systemic administration
- The limits of the use of corticosteroids are given by the adverse effects that may occur increased intraocular pressure, cataracts, eye pain, intraocular infections.
- The indications for the use of corticosteroids in retinal pathology are diverse: neovascular AMD, diabetic macular edema, macular edema in venous occlusions, posterior and intermediate uveitis.

Anti-VEGF Medication

- Indications
  - treatment of exudative AMD

  - macular edema from diabetes or from venous occlusions
  - CSCR
  - proliferative retinopathy from diabetes, sickle cell disease, prematurity

- The role of VEGF in angiogenesis
  - During embryogenesis, blood vessels are formed by two distinct processes [4]:

    Vasculogenesis, which involves the "de novo" differentiation of endothelial cells from mesodermal precursors, is characteristic of embryonic development and leads to the formation of primitive vascular plexuses.
    Angiogenesis involves the generation of new vessels from pre-existing ones; it involves a complex cascade of stimulatory and inhibitory factors; VEGF, growth hormone (GH) and insulin-like growth factor (IGF) are involved in ocular angiogenesis and CNVM formation

Vascular endothelial growth factor (VEGF) is normally present in retinal tissues and has higher concentrations in RPE. In normal eyes, VEGF has a protective role in maintaining adequate blood flow to the RPE and photoreceptors. Alteration of blood flow in the choriocapillaris, oxidative stress and degradation of Bruch's membrane are triggers for the initiation of VEGF overexpression in the RPE and in the retina.

The therapy with anti-VEGF drugs aims at two aspects: the anti-angiogenic effect and the anti-permeability (the action inside the CNVM is to inhibit the CVN and favor the resorption of the extravascular fluid) [9].

- The goals of anti-VEGF treatment are:
  - stabilization of visual acuity.
  - inhibition of neovessel proliferation.
  - fibrovascular scar modeling.
  - improving visual acuity.
  - elimination of subretinal fluid.
  - reduction of macular edema.

Currently, three anti-VEGF drugs are approved by the relevant international agencies for ophthalmic use: pegaptanib sodium, ranibizumab and aflibercept.

Bevacizumab is another anti-VEGF approved for systemic administration, and there are many others still in the experimental phase such as squalamine, Sirna-027, Cand5 (short interfering RNA), etc.

- ***MACUGEN (Pegaptanib sodium, Eyetech Pharmaceuticals)***
  - The mechanism of action is competitive antagonism, Macugen blocks the uptake of VEGF by endothelial cell receptors, inhibits the formation of neovessels and prevents leakage from already existing neovessels.
  - It is injected intravitreally (remains active in the vitreous for 28 days); the dose is 0.3 mg; injections are repeated every 6 weeks.
  - The limits of this method are mainly given by the high cost of the substance, the large number of injections and the need sometimes to associate PDT.

- ***LUCENTIS (Ranibizumab; RhuFab V2; Genentech- Novartis)***
  - It is injected intravitreally (the half-life in the vitreous is 3.2 days); the dose is 0.4 mg; injections are repeated every 4 weeks.
  - The complications described were minor: those related to the intravitreal injection (endophthalmitis—0.6%, cataract, retinal detachment, vitritis, uveitis—0.6%).
  - The limits of the treatment are represented by the still prohibitive costs as well as the need for too many intravitreal injections, repeated at too short an interval (one month) over a relatively long period of time (24 months). Recently, however, an intrascleral device has been approved that functions as a slow-release reservoir of Lucentis and can be refilled at 24-week intervals (*Susvimo; Roche*).
- ***AVASTIN (Bevacizumab; RhuMab VEGF; Genentech- Novartis)***
  - For intravitreal administration, 1.25 mg (0.05 mL) is injected; the injections are repeated every 4–6-8 or 12 weeks. The monthly treatment regimen over a period of 12–24 months seems to be the most effective, but many authors recommend monthly treatment for the first three months, and then whenever needed.
  - The vitreous half-life is almost double that of ranibizumab (5.5 days).
  - The advantages of using Avastin in the treatment of neovascular AMD are largely due to its low price (about 200 times cheaper than other anti-VEGF agents) without neglecting the efficiency and safety profile, thus allowing access to patients without financial possibilities to this therapy [11].

At the moment, there are many ophthalmological centers around the world that use Avastin in intravitreal administration. The reported results are favorable, but the manufacturer does not want to confirm the use of the substance in ocular pathology. Thus, this variant of therapy is practiced "off label"—outside the manufacturer's indication, but by the consensus of the specialists [12].

- ***EYELEA (Aflibercept; VEGF-Trap; Regenron-Bayer)***
  - Aflibercept blocks angiogenesis both by directly inhibiting VEGF-A and by inhibiting PlGF and VEGF-B, which otherwise act proangiogenically by stimulating VEGF-A.
  - and 2 studies [13, 14] showed that EYLEA improves and maintains vision, with administration once every 2 months, after the first 3 injections administered monthly, without requiring intermediate monitoring .
- ***BEOVU (Brolucizumab; scFv; Novartis)***
  - HARRIER [15] studies showed that BEOVU improves and maintains vision, with administration once every 3 months, after the first 3 monthly injections.

- ***VABYSMO (Faricimab-svoa; Roche)***
- Among the products of the following generations of anti-VEGF [5–8] we mention:
- ***EVIZON (Squalamina, Genaera)***
  - It is part of the class of aminosterols, a category of natural compounds with pharmacological properties; squalamine interrupts several aspects of the angiogenic process
- ***RNA INTERFERING AGENTS***
  - Small Interfering RNA (siRNA)—BEVASIRANIB
  - Bevasiranib is the first product in its class (siRNA), and its action is to suppress RNA translation by inactivating messenger RNA (mRNA).
  - SIRNA-027 (SIRNA Therapeutics Inc.) targets the VEGFR-1 mRNA receptor, which is found on vascular endothelial cells and is stimulated by both VEGF and PLGF.
- ***TYROSINE-KINASE INHIBITORS of VEGF receptors***
  - Oral administration of PTK-787 (VATALANIB)
  - This treatment can prevent the development of neovessels.
  - PAZOPANIB (GW786034 – GlaxoSmithKline) is a tyrosine-kinase inhibitor with multiple targets of the second generation that acts on all VEGFR, PDGFR α and PDGFR β receptors .
- ***PIGMENT EPITHELIAL DERIVED FACTOR (Pigment Epithelial-Derived Factor – PEDF)***
  - The major difference compared to other therapies is the possibility of protecting photoreceptors, damaged by abnormal blood vessels, simultaneously inhibiting the growth of these vessels.
- ***MICROTUBULE INHIBITORS ("vascular disruptors")***
  - ZYBRESTAT could be administered topically, in drops or in another form, and reach a sufficient concentration in the posterior pole to have therapeutic effects.
- ***ANTI-INFLAMMATORY AGENTS***
  - The pathogenesis of choroidal neovascularization includes inadequate production of proinflammatory cytokines, growth factors and proteolytic enzymes.
  - Since synthetic, non-peptide agonists of PPAR γ are easy to synthesize and cheap to formulate, yet another therapeutic possibility for AMD patients and beyond is envisioned, which has a great advantage – low cost.
- ***COMPLEMENT INHIBITORS***
  - The complement system is a key component of primary immunity.

  - Most studies have demonstrated that the process of drusen formation includes inflammatory processes and immune-mediated events.
  - TT30 or labeled Factor H, which would have the role of selectively delivering complement inhibitors to the loci where its activation would occur, thus controlling inflammation.
  - anti-C5 aptamer, ARC1905 that prevents activation of key terminal fragments (C5a and C5b) by inhibiting C5, could provide therapeutic benefits in both dry and wet forms of AMD.

- ***FENRETINIDE***
  - Fenretinide is a drug originally intended for the treatment of certain forms of cancer, rheumatoid arthritis, acne, and psoriasis, and has recently found applications in the treatment of severe eye diseases such as Stargardt's disease and AMD dry form.
  - Fenretinide blocks the accumulation of toxins derived from retinol (vitamin A) due to its high affinity for a retinol-binding protein.

- ***RAPAMICIN***
  - Rapamycin, a macrolide fungicide with antimicrobial and immunosuppressive properties, also exerts important antitumor and antiangiogenic actions.

Combined Therapies

- It seems to be a logical solution to combine several therapeutic lines to engage the various processes involved in the formation and maintenance of CNVM.
- Anti-VEGF medication is an important part of the therapeutic arsenal, but also other targets for therapy seem to be very important, such as: platelet-derived growth factor (PDGF), tissue necrosis factor alpha (TNF α), or fibroblast derived growth factor (FDGF).
- Nonspecific drugs such as corticosteroids can block these factors, but it is known that these therapeutic agents have a series of adverse effects, which should not be neglected.
- The combination already used in exudative AMD is anti-VEGF medication associated with photodynamic therapy (PDT); there are no conclusive data to confirm the effectiveness of this combined therapy in terms of improving visual acuity, but there are a number of reports related to the reduction in the number of intravitreal injections when combining PDT.
- The choice of a combined therapy must consider several objectives: improving the visual prognosis, reducing the frequency of treatment and potentially reducing the total risk of adverse effects.
- The combined therapy aims to: mediate thrombosis of the neovascular network, block the angiogenic stimulus, additive effects of the substances, reduce the retreatment rate, maintain choriocapillary perfusion and improve the visual

prognosis. Thus Verteporphyrin-PDT was associated with ranibizumab (FOCUS), with pegaptanib, with bevacizumab, with triamcinolone acetonide (VERITAS, VisTA, RETINA, VERTACL), with anecortav acetate (C-00-07).
- Another promising therapeutic association is represented by the combination of brachytherapy with the use of antiangiogenic agents injected intravitreally. Combining the two effects can allow a faster and better recovery of visual function.

Antioxidant Medication

- It especially has a prophylactic role, in preventing the appearance of advanced forms of AMD as well as in slowing down the progression of the disease.
- A treatment proven effective in preventing advanced forms of AMD is the formula containing vitamin C (500 mg), vitamin E (400 IU—international units), beta-carotene (15 mg), zinc oxide (80 mg) and copper (in the form of cupric oxide 2 mg) – AREDS formula (The Age-Related Eye Disease Study) [16]
  - reduces the risk of progression to advanced forms of AMD, defined as neovascular AMD or geographic atrophy with interest in the center of the macula
  - the role of omega-3 polyunsaturated fatty acids (EHA and DHA) in reducing the progression of AMD is real.

Gene Therapy

- It is a revolutionary therapeutic alternative, whose principle consists in the application of a functional gene to correct a genetic mistake or to introduce a new function into the pre-existing human cell, to treat a specific condition [17].
- The most important steps in gene therapy are the identification of the gene related to the respective condition, its cloning and its transfer to the target organ or cell. At the moment, somatic treatment is the most affordable [7].
- Treatment with somatic gene therapy can be of two types: in vivo and ex vivo. Eyelashes can reach the eye in three ways:
  - by in vivo injection of a vector derived from a virus, which expresses a therapeutic gene, directly into the affected retinal tissue.
  - by in vivo injection of genes carried by nonviral agents (liposomes).
  - by eye transplantation of ex vivo cells (cells extracted from the body and modified by genetic transfer).
- For the treatment of neovascular AMD, it is necessary to correctly choose the genes for transfer, so that they not only inhibit neovascularization, but also do not exert toxic effects on neighboring cells.

- **vectorial adenoviral**
  - Adenoviruses are the most used vectors in experimental eye gene therapy studies.
- **VEGF antagonists** (related to the principles of therapy gene)
  - The extracellular secreted domain of VEGF receptor 1, sFlt-1, is a natural protein, antagonistic to VEGF, formed by alternative splicing of the pre-mRNA, precursor of the entire receptor.
  - Intraocular injection of attenuated adenoviral vectors containing sFlt-1 (Ad.. sFlt-1) induced long-term suppression of CVN in mice and monkeys. Periocular injection of Ad.sFlt-1 led to transduction of the gene in episcleral cells, increased expression in the choroid and consequent suppression of CVN.
  - The gene transfer of sFlt-1 may be effective in the treatment of patients with neovascular AMD.
- **factor epithelial pigment derivative (PEDF)**
  - Intravitreal or subretinal injection of an attenuated adenoviral vector expressing human PEDF (AdPEDF.11) proved to be effective in suppressing the development of CVN, and even in inducing the regression of already established neovascularization.
  - Subconjunctival injection of AdPEDF.11 caused transduction of episcleral cells, which produced PEDF, with regression of CVN. Since subconjunctival injections are less invasive and obviously associated with much fewer adverse effects, they can be a useful alternative to intravitreal injections.
- **"Zinc Finger" proteins**
  - another way to obtain physiologically increased levels of PEDF is the expression of a "zinc finger" protein transcription factor (ZFP-TF), obtained by genetic engineering.
- **Angiopoietins**
  - Angiopoietins represent a family of extracellular ligands that recognize and bind to the extracellular domain of Tie-2, a tyrosine-kinase receptor specific to endothelial cells, with domains homologous to endothelial growth factor.
  - Angiogenesis appears associated with increased levels of angiopoietin-2 as it destabilizes, favoring the expansion of neovessels under the influence of VEGF or inducing the regression of the same neovessels when VEGF is absent
- **Angiostatin**
  - Angiostatin can be effective in the treatment of wet AMD, but obviously studies on human subjects will confirm or not the effectiveness of the method.

- **Matrix metalloproteinases**
  - Matrix metalloproteinases (MMP) are enzymes that degrade the extracellular matrix and contribute to tissue remodeling. MMPs appear to be involved in the pathogenesis of AMD, proliferative diabetic retinopathy, and retinopathy of prematurity.
- **TIME-3**
  - TIMP-3 may be a good candidate for gene therapy in exudative AMD, but expression of an insoluble protein carries more risks than expression of a soluble one.

AMD represents a health problem with global impact. Injectable treatment with anti-VEGF has undoubtedly represented an enormous gain in improving the quality of visual life of patients, and spacing the intravitreal injection intervals as widely as possible is salutary. New solutions in the sustained delivery of therapeutic agents that induce both the regression of macular lesions and facilitate the physiological regeneration of affected tissues are eagerly awaited.

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Chapter 18
Ophtalmological Pathology and Medical and Surgical Management in Eye Disease: Retinal Detachment

Simona Delia Nicoară

Abstract There are three types of retinal detachment: rhegmatogenous, tractional and exudative.

Rhegmatogenous retinal detachment (RRD) is caused by one or multiple retinal tears through which the liquid from the vitreous cavity passes, separating the neurosensitive retina from the retinal pigmented epithelium.

The risk factors for RRD are: old age, previous cataract surgery, myopia, positive familial history, peripheral degenerative retinal lesions, RRD in the fellow eye and ocular trauma.

The symptoms of RRD are specific, their onset respecting the chronology of pathogenetic events: perception of floaters corresponds to vitreous degeneration and detachment; repetitive and fixed photopsia signals the occurrence of a retinal tear; progressive amputation of the visual field evolves in parallel with the detachment of the retina; visual acuity decreases when the macular retina detaches.

The treatment of RRD is surgical and urgent, especially if the macula is on. Two major categories of interventions are used: ab externo (scleral indentation) and ab interno (pars plana vitrectomy). RRD has a good prognosis if it is operated on in time.

Tractional retinal detachment (TRD) is caused by tractions exerted by membranes in the vitreous or on the surface of the retina in the context of proliferative retinopathies, of which the most common one is diabetic retinopathy. The decision to operate depends on systemic and ocular factors and the visual prognosis should be discussed with the patient.

In exudative retinal detachment, the functioning of the outer blood-retina barrier is disrupted, with the accummulation of fluid under the neurosensitive retina**.** Treatment addresses the cause.

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Rhegmatogenous Retinal Detachment (RRD)

- Rhegmatogenous retinal detachment (RRD) is the most common form of retinal detachment, being a serious condition that must be treated urgently.
  - **RRD represents the separation of the neurosensitive retina from the underlying retinal pigmented epithelium (RPE) by fluid that penetrates from the vitreous cavity into the subretinal space through one ore multiple retinal defects—tears.**
- The incidence of RRD in the general population varies between 0.01% and 0.018%, it increases to 1% following cataract surgery and up to 4 times following YAG laser capsulotomy.
- The risk factors for RRD are: old age, history of cataract surgery, myopia and positive familial history (especially certain genetically transmitted diseases), peripheral degenerative retinal lesions, RRD in the fellow eye, ocular trauma.
- In the pathogenesis of RRD, the following events happen successively: vitreal syneresis, posterior vitreous detachment (PVD), producing the retinal tear (s), progressive detachment of the retina.

Posterior Vitreous Detachment

Pathogenesis

- **Posterior vitreous detachment (PVD) is the first step in the pathogenesis of RRD**.
  - It is a frequent, physiological, age related event, with a clinical picture which is similar to RRD.
  - **It is preceded by vitreal syneresis which consists of the progressive liquefaction of vitreous** (syneresis is earlier in myopes and people with connective tissue diseases). Thus, confluent, liquid spaces appear within the vitreous gel, followed by a breach in the posterior vitreous cortex through which the liquid passes in the space between the vitreous and the retina, producing the PVD.
  - Vitreo-retinal adhesion is very high at the vitreous base, which is why at this site the vitreous remains attached to the retina, **the detachment always starting from the posterior part:** posterior vitreous detachment (PVD).
  - Vitreous detachment may occur gradually (85% of cases) or suddenly (15% of cases).

  - The risk of producing a retinal tear is significantly higher in acute PVD (10–15%). The liquid from the vitreous cavity seeps through the retinal tear, progressively detaching the retina.

- ***Symptoms***
  - The perception of floaters is the specific symptom of vitreal syneresis.
  - Acute PVD always manifests itself clinically by the sudden perception of floaters.
  - If the acute PVD is complicated with vitreous hemorrhage, floaters are denser or, if the hemorrhage is important, vision suddenly decreases.
  - Chronic PVD may go unnoticed or manifest itself by transient floaters.
- ***Signs on fundus examination:***
  - Weiss ring—detached vitreous at the optic disc
  - Posterior hyaloid visible and detached from the retina
  - Occasionally vitreous hemorrhage.

Ocular ultrasound shows an echogenic, linear membrane in the posterior part of the vitreous cavity, freely movable to the movement of the eyeball. Over time, this mobility can diminish.

Complications

- The most serious complication of PVD is the retinal tear, for the identification of which the periphery of the retina must be examined very carefully over 360 degrees. It should be noted that more than half of retinal detachments have more than one retinal tear.
- Vitreous hemorrhage can occur alone or in association with one or more retinal tears. Its presence makes it difficult to examine the retina in order to identify possible tears.

Attitude

- **Any person with the specific symptoms of PVD (floaters) should be carefully examined with the pupil maximally dilated to identify or exclude retinal tears**.
  - If no retinal tear is identified, the patient is monitored and instructed to go to the doctor as soon as he notices an increase in floaters, a progressive amputation of the visual field or a decrease in visual acuity.
  - **If one or more retinal tears are identified and the retina is still not detached, they must be blocked urgently, either by laser photocoagula-**

tion or by transscleral cryoapplications, and the patient must be carefully monitored for the next period.

– If vitreous hemorrhage is associated, the retinal periphery is examined under the given conditions and ocular ultrasound is performed to identify or rule out retinal tears/detachment. The patient is re-examined in the following days, with the hope that resorbtion of the intravitreal hemorrhage will improve visualization of the peripheral retina.

- **Not all PVDs are followed by RRD.** There are areas where the vitreous-retinal adhesion is abnormally high and where the risk of retinal tear is higher.
- **Risk factors related to the structure of the retina that make it more vulnerable to a PVD**.

Peripheral Retinal Degenerations

Peripheral retinal degenerations can be classified according to the retinal layers in which they occur: vitreoretinal, intraretinal and chorioretinal. **Vitreoretinal degenerations present the greatest risk for RRD.**

Vitreoretinal Degenerations

Lattice Degeneration

- RRD occurs in 1% of people with lattice. Its frequency is 30% in RRD and 6% in the general population.
- It is associated with myopia and connective tissue diseases (Stickler's).
- Appears as areas where the retina is thinned and has some white crossing lines, with or without round holes, typically circumferentially oriented (in Stickler's disease they can be oriented radially).
- Retinal tears occur at the posterior extremity and at the edges of the degenerative lesion where the vitreoretinal adhesion is maximum.
- If the degenerative lesions are discovered by chance, being asymptomatic, they should not be treated.
- The only indication for laser photocoagulation is lattice lesions in people with RRD in the fellow eye.

Snail Track Degeneration

- Is frequent in myopes, being considered an early stage of lattice degeneration and appears as an area of thinned retina with a glossy appearance and circumferential orientation, with or without round holes in the surface.

Peripheral Retinal Tufts

- They are caused by traction on the retina by the vitreous and can be cystic, noncystic and zonular.

Peripheral Retinal Holes

- They are full thickness retinal defects due to atrophy, not vitreoretinal traction, and may be associated with lattice and snail track degeneration.

Intraretinal Degenerations

Degenerative Retinoschisis

- Represents a separation of the layers of the neurosensitive retina produced by fluid, more frequent in hypermetropes after the age of 40, with temporal localization, bilaterally.
- It is asymptomatic, and in the visual field it is manifested by absolute scotoma.
- During the fundus examination, the separation of the retinal layers is highlighted, with the inner layer protruding into the vitreous cavity like an immobile balloon.
- When the sclera is indented at the retinoschisis site, its external sheet becomes white and acquires a reticular appearance.
- It is the cause of RRD in 0.05–2.5% of cases.
- It should only be treated if the patients are symptomatic or there is a threat of macula.

White with and Without Pressure

- They are benign degenerations, with a very low risk of RRD. The peripheral retina appears whitish without/with pressure, being found in 30–35% of normal eyes.

Cystoid Peripheral Degeneration

- Appears in the form of small yellowish vesicles with imprecise boundaries that can fuse to form cavities in the outer plexiform layer.

Snowflakes Degeneration

- It has a rare prevalence and is characterized by the presence in the periphery of the retina of small deposits, simlar to snowflakes, more frequently arranged in the superotemporal quadrant.
- It may be associated with lattice degeneration, retinoschisis, white without pressure.

Chorioretinal Degenerations

Paving Stone Degeneration

- It is characterized by the presence of areas of chorio-retinal atrophy that are white-yellow, with a pigmented outline, sometimes imprecise, located more frequently in the inferonasal and temporal quadrants, between the ora serrata and the equator. The prevalence varies between 4 and 28% and they are benign lesions that do not cause complications.

Peripheral Retinal Drusen

- They are benign, age related lesions, consisting in lipoprotein deposits located between the RPE and Bruch's membrane, Sunt leziuni benigne, legate de vârstă, constând în depozite de lipoproteine între EPR și membrana Bruch, produced by degeneration of the RPE cells. They appear in the form of small, round and precisely defined crystals.

Retinal Tears

Retinal Hole

The hole is a full thickness retinal defect caused by atrophy, not vitreo-retinal traction. Retinal holes may be seen in areas of lattice or snail track degeneration. Sometimes the free—floating operculum is identified in the vitreous near the hole, witnessing its production by traction from the vitreous.

Retinal Tear

It is a full thickness retinal defect produced by traction during PVD. The persistance of vitreous traction at the edges of the tear keeps it open, which leads to retinal detachment. Tears occur in areas where vitreoretinal adhesion is high or at the limits of a lattice zone and may be U-shaped or fish-mouth shaped. Sometimes the tear is crossed by a retinal vessel.

Particular forms of retinal tear

Retinal Dialysis

It is a circumferential retinal disinsertion at ora serrata, often being posttraumatic. Because it does not follow a PVD, the progression of RRD produced by retinal dialysis is slow, the vitreous being solid (gel).

Giant Retinal Tear

It affects more than 3 clock hours and occurs at the posterior border of the vitreous base. Unlike retinal dialysis, the giant retinal tear is produced by PVD, the vitreous remaining attached to the anterior, undetached retina. The risk factors for giant retinal tear are: high myopia, trauma, Marfan syndrome, Stickler syndrome.

Clinical Picture in RRD

Symptoms

- The symptomatology of RRD is specific, the onset of symptoms respecting the chronology of pathogenetic events:
- The first symptoms are the perception of floaters corresponding to vitreous degeneration and PVD.
- Repetitive photopsia follows, located in the same place, better visible in low light conditions.
- This translates the production of retinal tear.

- Progressive amputation of the visual field corresponds to the progression of retinal detachment.
- Visual acuity decreases when the detachment affects the macular retina.
- A particular clinical picture is present in retinal dialysis which, not being preceded by PVD, does not reveal floaters and phosphenes, being discovered either by chance or when the visual field and visual acuity are affected.

Signs
- The fundus examination reveals vitreous and retinal signs, to which other signs are sometimes added.

Vitreal Signs
- Weiss ring represents the disinsertion of the vitreous at the level of the optic disc.
- Pigment cells in the vitreous cavity (tobacco dust) indirectly translate the presence of retinal tear with the release of RPE cells in the vitreous.
- More or less heavy bleeding in the vitreous is not mandatory.

Retinal signs
- Retinal tear: the shape (U, fish mouth, hole, dialysis), number, location, size (small, medium, large, giant) are described.
- The detached retina appears grayish, convex, dome—shaped, extended to the periphery, more or less mobile (depending on the age of RRD), more or less bullous (depending on the amount of subretinal fluid), more or less extensive, with or without macular involvement. If RRD is produced by a macular hole or a posterior tear, the retina is more prominent at the posterior pole. There are signs that attest to the age of RRD: thinning of the retina, the presence of demarcation lines (appear in RRD older than 3 months), intraretinal cysts (older than 1 year), proliferative vitreoretinopathy (PVR).

Other Signs
- In extensive RRD, an associated pupillary defect may occur, due to the massive destruction of ganglion cells.
- Intraocular pressure is usually low, but can be normal or even elevated.
- In less recent RRD, inflammatory signs can be identified at the level of the anterior segment, which makes RRD often misdiagnosed as anterior uveitis.

Lincoff's Rules for Locating Retinal Tears

Superior RRD
- In supero-nasal or supero-temporal RRD, the tear is usually located near the superior margin of the detachment.
- If the RRD is symmetrical, the tear is around the 12 o'clock meridian.

Inferior RRD

- The tear is usually in the part where more fluid is accumulated, but it can be even at the level of 6 o'clock meridian.

Complications

- **The major complication of RRD is proliferative vitreo-retinopathy (PVR)** which obscures the anatomical and functional prognosis of this condition. It consists of a pathological process characterized by cell proliferation with the formation of contractile membranes in the vitreous, on both sides of the retina, as well as intraretinal, with retinal shortening.

Pathogenesis

- Essential cells in the genesis of VRP are: RPE cells, glial cells, fibroblasts and macrophages.
- The separation of the neuroepithelium from the RPE and implicitly from the choriocapillaris is followed by ischemia that determines the change in the polarity of the RPE cells and their passage through an epithelial-mesenchymal transformation process that consists in the loss of the epithelial cell phenotype in favor of a mesenchymal cell.
- Various chemokines and cytokines whose presence is made possible by the loss of functionality of the blood-retinal barrier induce cell proliferation, migration and contraction. The cells become similar to fibroblasts containing actin and myosin and having the ability to contract.
- Müller are activated causing marked intraretinal gliosis with increased stiffness and shortening of the retina.
- Macrophages fulfill multiple roles: secretion of enzymes and growth factors, as well as differentiation into fibroblast-like cells. Genetic factors may also intervene to explain the predisposition to PVR in some patients with RRD.

PVR Classification

- Over time, several classifications of PVR have been developed, quite cumbersome and difficult to apply clinically. Therefore, most clinicians prefer to characterize PVR as mild, moderate, or severe.

Ocular Ultrasound

- Although the diagnosis of RRD is clinical, in situation where examination of the posterior segment of the eye is impossible (cataract, vitreous hemorrhage), ocular ultrasound is mandatory.
- Detached retina appears as a convex, irregular membrane with increased reflectivity, mobile when the eyeball moves. If PVR has already been installed, the detached retina has reduced mobility, is more or less rigid.

Treatment

The Treatment of RRD is Surgical

The Moment of Surgery

- The degree of urgency depends on the appearance of the macular retina, as functional outcomes have been observed to be significantly better in retinal detachments with macula on.
- If the macular region is still not detached and the retinal tear is U-shaped (detachment is progressing rapidly), the operation should be performed as soon as possible to avoid detachment of the macular region.
- If the macular region is already detached, the degree of urgency is lower, demonstrating similar functional results after all operations performed within the first 7 days of diagnosis in this category.

Posture

- The particular positioning of the patient in the preoperative period is intended, on the one hand, to remove the fluid from the macular region and on the other, to facilitate the surgical intervention.
- Thus, in superior bullous DRRs, the patient is positioned supine, with the homolateral cheek on the pillow (temporal DRRs) or with the contralateral cheek on the pillow (nasal DRRs). In DRRs with giant tears, the goal of patient positioning is to unfold the tear.

Surgical Intervention

- **In the treatment of DRR, two major categories of surgical interventions are used: ab externo (scleral indentation) and ab interno (pars plana vitrectomy—PPV). In recent years, there is a tendency to use PPV in all DRRs**. In both categories of surgical techniques, sealing the retinal tear is crucial and can be achieved by cryoapplications or by laser endophotocoagulation which is only accessible in PPV.
- ***Ab externo* surgery** aims to bring the eye wall closer to the retina by suturing at the sclera some indentation materials. This technique is **indicated in simple RRD, being of election in RRD without PVD (retinal dyalisis)**. Technically, indentation can be:
- Segmental, if the tear is unique or there are several tears, but located within one clock hour;
- Cerclage (circumferential band) or several segmental indentations, if there are more tears.

- **PPV** is the **indication of choice in: RRD with posterior tear, multiple tears, giant tear,** RRD on aphakic/pseudophakic eye, RRD complicated with PVR. Since the main cause of failure of RRD surgery is an unidentified tear, PPV is the technique preferred by most vitreoretinal surgeons at the moment, offering ideal conditions for intraoperative visualization of the retina and implicitly for the identification and treatment of all retinal tears.

Prophylactic treatment:

- U-shaped tear following a symptomatic acute PVD
- Retinal dyalisis
- Fellow eye in case of RRD with giant retinal tear
- Lattice degeneration in case of RRD on the fellow eye
- Associated with risk factors: myopia, aphakia.

  – RRD has a good prognosis if operated on in time
  – Urgency <24 h—RRD with macula on
  – Mandatory—careful examination of the retinal periphery in all patients with acute PVD.

Tractional Retinal Detachment (TRD)

TRD is the separation of the neurosensitive retina from the underlying RPE due to tractions exerted by membranes in the vitreous or on the surface of the retina. The causes are varied, the most common being diabetes mellitus. All conditions that cause TRD are proliferative retinopathies. Table 2.2 summarizes the causes of TRD in adults and children (Table 18.1).

Classification of TRD

TRDs can be classified according to several criteria as follows:
Depending on the macular involvement: macular or extramacular.
Depending on the need for surgery:

- surgical: involves the posterior pole or the superior periphery;
- nonsurgical: involves the inferior periphery.

Ophthalmological Evaluation

- Alignment of the eyeballs: long standing TRDs can cause sensory exotropia which is a clue for poor prognosis.
- Pupilary reflex: afferent pupilary defect is a clue for poor prognosis.
- Iris and anterior chamber angle are examined prior to pupil dilation to identify possible new vessels.
- The state of the lens is important in order to prepare the operative strategy whihc, in the presence of cataracts, must include the extraction of the lens.
- The examination of the retina must identify: the precise localization of the fibrovascular membranes, of neovascular tufts, of large vascular membranes, the areas of retinal tractional detachment, the subretinal fibrous bands, the presence of pre and subretinal blood. It is possible that the traction causes the formation of one or more retinal tears, in which case the detachment is combined (mixed). The

Table 18.1 Causes of TRD

Adults	Proliferative diabetic retinopathy
	Retinal vein occlusions
	Retinal vasculitis
	Trauma
	Sickle cells retinopathy
	Uveitis
	Proliferative vitreoretinopathy
Children	Complications of retinopathy of prematurity
	Familial exudative vitreoretinopathy
	Persistence of fetal vascularisation
	Toxoplasmosic retinitis
	Toxocariasic retinitis
	Sickle cells retinopathy
	Trauma
	Proliferative vitreoretinopathy
	Incontinentia pigmenti

existence of the tear in the TRD is signaled indirectly, even without its visualization, by the convex surface of the detached retina due to the subretinal fluid. Intraoperatively, the tear is usually identified at the base of an area of maximum antero-posterior traction. In case of identification of a combined mechanism of detachment (tractional and rhegmatogenous), the operation must be urgently planned.

Ocular ultrasound is very important in TRD because it highlights the following essential signs for planning the operation and formulating the prognosis:

- Identifies areas of retinal traction and detachment.
- Shows the state of the posterior vitreous: detached or not.
- Demonstrates the presence of intravitreal, subretinal or preretinal hemorrhage.

Treatment

Systemic Treatment

- Since TRD often occurs as a complication of various systemic conditions, their treatment has an essential role and includes: balancing diabetes, hypertension, nephropaties and hemoglobinopathies.

Surgical Treatment

- The decision to operate a TRD or not depends on several factors, both systemic and ocular, and the visual prognosis should be discussed with the patient preoperatively.

- **VPP in TRD is one of the most difficult vitrectomies and requires experience and a good understanding of the pathogenetic mechanisms of the disease**. The introduction of minimally invasive PPV into clinical practice has considerably improved the prognosis of TRD.
- The factors on which the operative indication in TRD depends refer to the state of the macula: if it is detached or threatened, then PPV must be performed.

The Role of Anti-VEGF Preoperatively
- Although there is no consensus on preoperative injections of anti-VEGF, these substances reduce intraoperative bleeding in case of significant vascular proliferations, making dissection of the membranes much easier.
- If fibrous proliferation predminates at the expense of the vascular one, then the preoperative administration of anti-VEGF can be risky due to the increased contraction of the fibro-vascular membranes. In general it is recommended that anti-VEGF injections be given 3–5 days before surgery in TRD.

The Role of Preoperative Panretinal Laser Photocoagulation
- If possible, laser panfotocoagulation of the retina before PPV is especially indicated for patients who have not received this treatment in the past.
- Laser photocoagulation at a safe distance from the base of the fibrous membranes facilitates the induction of PVD, thus facilitating intraoperative dissection of the membranes.
- Additionally, the operative time required to complete retinal laser endophotocoagulation is shortened.

The surgical intervention includes **vitrectomy, membrane dissection, laser photocoagulation of the retina and the introduction of a tamponade agent.**

Complications
- Progressive retinal ischemia and the atrophy of the photoreceptors layer.
- Progressive retinal ischemia can lead to iris and angle neovascularization with neovascular glaucoma.

Complications of surgery are: vitreous hemorrhage, secondary intraocular hypertension, recurrent retinal detachment, cataract and neovascular glaucoma.

Exudative Retinal Detachment (ERD)

ERD represents the disruption of the functioning of the outer blood-retina barrier, with the penetration of fluid under the neurosensitive retina and its separation from the RPE.

Symptoms
- If the macular region is affected, metamorphopsias and fluctuations in visual acuity occur.
- Relative visual field defect and floatersmay occur in case of vitritis.

Signs

- The detached retina appears as a dome with a smooth, convex, more or less prominent surface.
- In bullous detachment, fluid moves rapidly with position and may be clear / cloudy (rich in lipids).
- **In ERD there are no retinal tears and no traction on the retina**.
- Evidence of possible previous detachments can be highlighted in the form of irregular pigmentation, as well as signs of the underlying disease (for example, Coats disease).

Investigations and Treatment

- All patients with ERD should undergo a complete ophthalmic and systemic examination, blood and urine tests should be performed.
- Ultrasouns is always indicated, highlighting a possible posterior scleritis.
- Treatment addresses the cause.

The causes of ERD are summarized in Table 18.2.

Retinoschisis

Definition and Classification

- **Retinoschisis is a separation in the layers of the retina.**
  - There are two types of retinoschisis:
  - ***degenerative***, found in 5% of normal adults, generally hyperopic, bilateral;
  - ***juvenile X- linked***.
- Depending on the location of the retinal detachment, retinoschisis can be:
  - Typical: separation between outer plexiform and inner nuclear layer
  - Reticular: separation within the nerve fiber layer.

Degenerative Retinoschisis

- Symptoms
  - Degenerative retinoschisis is asymptomatic. It has an absolute defect in the visual field.
- Signs
  - The separation of the retina appears as a balloon that protrudes into the vitreous cavity, frequently located in the infero-temporal quadrant, in an area of peripheral cystoid degeneration.

Table 18.2 Causes of ERD

Congenital	Nanophthalmia Mucopolysaccharidoses Familial exudative vitreoretinopathy	
Acquired	*Vascular*	Exudative Age Related Macular Degeneration Coats Central Serous Chorioretinitis Vasculitis Malignant hypertension Pre-eclampsia
	Tumoral	Choroidal tumors
	Inflammatory	Posterior uveitis Posterior scleritis Postoperatively Extensive panretinal laser photocoagulation Orbital cellulitis Idiopathic inflammatory orbital disease

– If the scleral wall is indented at the level of the retinoschisis, the whitening of its external sheet is highlighted, sometimes with a reticular appearance.

The diagnosis is clinical.

The most important ***differential diagnosis*** is made with chronic RRD. The criteria for differentiating the two entities are presented in Table 18.3.

Complications

- In evolution, retinoschisis may develop tears of the inner leaflet that are small and round or much less often, of the outer leaflet.
- If tears occur in the outer leaflet, the risk of RRD is reduced, whereas if tears occur in both the inner and outer leaflets of the retinoschisis, the risk of RRD is increased.

Treatment

- Retinoschisis is kept under observation. Surgery is only indicated if retinoschisis is complicated by RRD.

Juvenile X-Linked Retiboschisis

- **It is a rare condition caused by an abnormal intercellular adhesion molecule (located on Xp22), which leads to separation in the retinal nerve fiber layer**.
- Occurs in men, can begin in childhood with maculopathy, having a reserved functional prognosis.

Clinic

- The fundus examination shows foveal schisis, characterized by cystoid spaces similar to cystoid macular edema, but without leakage on angiophluorography.
- Macular atrophy occurs in late stages.
- If the confluence of the holes in the inner sheeet of a peripheral retinoschisis occurs, free retinal vessels are visualized in the vitreous body.

Investigations

- Scotopic ERG reveals the selective loss of the B wave, and the visual field examination shows an absolute defect in the area corresponding to the retinoschisis.
  Prophylactic treatment is controversial, as it may favor RRD.

Choroidal Detachment and Uveal Effusion Syndrome (Table 18.4)

Clinic

- Convex domes, smooth, of normal/darker retinal color, located in the extreme periphery, whose posterior extension is limited by the vortex veins
- They can touch (*kissing choroidals)* → retinal detachment.

Treatment

- Observation
- Treatment of the cause
- Surgical drainage—after liquefaction of the clot (10–14 days).

Uveal effusion syndrome is produced by:

- Idiopathic detachment of the retina, choroid, ciliary body, usually associated with a thicker sclera; it mainly affects healthy men.
- Classification in three types:
  - 1—nanophthalmic eyes
  - 2—non-nanophthalmic eyes, with clinically abnormal sclera
  - 3—non-nanophthalmic eyes, with clinically normal sclera.

Clinic: exudative detachment of the choroid and retina (Table 18.5).

Treatment

- Drainage → decompression
- Favorable prognostic factors: nanophthalmia, rigid sclera.

Table 18.3 Differential diagnosis retinoschisis—chronic RRD

Characteristic	Retinoschisis	Chronic RRD
Vitreous	Clear	Pigment ± blood
The dome	Smooth convex	Irregular convex
Laterality	Usually bilateral	Unilateral
Visual field defect	Absolute	Relative
Signs of chronicity	Without demarcation line	With demarcation line
Tears	Without/small, on the inner sheet	+
Laser	Well visible effect	No effect

Vitreous Hemorrhage

- Vitreous hemorrhage—VH—is the accumulation of blood in the vitreous cavity as a result of the rupture of blood vessels:
  - Normal retinal vessels:

    Retinal tear 11–44%
    Retinal detachment
    Trauma
    Retinal vessel rupture during posterior vitreous detachment—PVD.
  - Abnormal retinal vessels, altered in: diabetes, atherosclerosis, coagulation disorders.
  - Rupture of new vessels due to the increase in hydrostatic pressure, trauma.
- The incidence of VH is higher in:
  - men
  - patients under anticoagulant treatment
  - VH associated with proliferative diabetic retinopathy—PDR, central retinal vein occlusion—CRVO.
- VH is located in the closed vitreous cavity and is limited by the inner limiting membrane (ILM) of the retina posteriorly, laterally by the non-pigmented epithelium of the ciliary body and the Zinn zonule and anteriorly by the posterior capsule of the lens.
- **Spontaneous vitreous clearing is done according to the causative disease, recurrence or bleeding tendency, syneresis.**
- Complications of the non-clearing VH lead to hemosiderosis, retinal fibrovascular proliferation, secondary hemolytic and ghost cell glaucoma.
- Symptoms
  - The onset of VH is brutal with unilateral, painless decrease of VA to light perception or visual blurring in the form of a black veil in the front of the eye.
  - In early, lower volume VH, black mobile dots are present in the visual field.
  - The pupillary red reflex is absent if the VH is voluminous.

Table 18.4 Choroidal detachment

Effusion	Hypotony Excessive panretinal laser photocoagulation Excessive cryotherapy Posterior uveitis Nanophtalmia
Hemorrhage	Intraoperatively Traumatic Spontaneous

Table 18.5 Ultrasonic characteristics of vitreo-retinal diseases. Differential diagnosis

PVD	Posterior hyaolid: poor reflectivity, may appear discontinous unless the eye is in motion Eye movement → staccato movement of the hyaloid, with a latency of 1s Module A—low reflectivity Color: without blood
RRD	Convex, irregular, high reflectivity membrane Eye movement → undulatory movement of the membrane (exception: PVR) Module A—high reflectivity Color: blood
TRD	High reflectivity membrane that forms vitreous tent Eye movement does not produce membrane movement Color: blood
Choroidal detachment	Dome-shaped membrane, regular surface, high reflectivity Attached to the vortex veins Color: blood in the retina and choroid
Vitreous hemorrhage	Reflective material in the vitreous cavity (as in vitritis)

- VH has multiple causes and variable clinical manifestations depending on the causative condition:
  - Most frequently VH is present in:

    PDR
    PVD with/without retinal tear
    trauma

  - More rarely VH is present in:

    CRVO
    Arterial macroaneurysm
    Hemoglobinopathies
    Age related Macular Degeneration
    Intraocular tumors

- The clinical signs and evolution of VH are correlated with the quality of the vitreous and the amount of accumulated blood.
  - Fundus examination

    Can be performed if VH is not dense.
    Requires examination by indirect ophthalmoscopy and scleral depression of the periphery in order to highlight the retinal tears.
    Indirect ophthalmoscopy highlights:

    Low volume VH: black shadows in the red ophthalmoscopic field
    Difuse VH: the back of the eye is blurred, without the ability to assess ophthalmoscopic details of the retina and vitreous.

Total VH

- The back of the eye cannot be examined
- The red pupillary reflex is absent

Bleeding may occur in the retrohyaloid space, sângerarea în spațiul retrohialoidian Berger, Petit produce un menisc catacteristic vizualizat la lampa cu fantă
Acute PVD with VH has a 70% risk for retinal tear.
A and B ultrasound:

Allows examination of the vitreous cavity, vitreo-retinal interface and chorioretinal layer.
Differentiates recent from old VH.
Highlights the retinal tear, RRD, TRD
It is an important element of clinical diagnosis, assessment of disease prognosis and is useful for choosing the best therapeutic strategy.
Ultrasound must be repeated every 8–10 days.

- The clinical evolution of VH depends on:
  - localisation
  - causes
  - severity of the bleeding
- Patients with diabetes and AMD have the worst prognosis.
- **Absorbtion of blood from the vitreous is a very slow process.**
  - **Complete absorbtion** of VH without vitreous organization and complete vitreous clearing may take **6–8 weeksi,** the blood being eliminated with a rate of 1% per day; if bleeding persists over 6–8 weeks, spontaneous absorbtion is no longer possible.
  - The hemorrhage may become organized with the formation of white-yellow bands, present in persistent or recurrent bleeding.
  - Complications such as vitreous liquefaction and vitreous degeneration can occur.
  - Proliferative retinopathy can lead to TRD by the organization of residual strands within VH.
- Complications are more frequent and severe in long standing and relapsing VH:
  - Secondary glaucoma:

    Hemolytic glaucoma in which macrophages containing red blood cells debris and hemosiderin block the trabecular meshwork.
    Ghost cell glaucoma in which the trabecular meshwork is blocked by degenerated and rigid red blood cells, with no or very few macrophages or red blood cells debris.

  - Hemosiderosis bulbi—iron from hemoglobin is toxic for the photoreceptors

  - In people with high myopia there is a risk of retinal tears and RRD.
  - Proliferative retinopathy can lead to TRD

- Traumatic VH is produced by:
  - Retinal, choroidal, scleral rupture
  - Uveal lesions
  - Optic nerve head avulsion**Clinical observation and follow up of the patient with VH**

- Spontaneous clarification of the vitreous, and/or under medical treatment, is sought in days, weeks
- Repetead ultrasonography
- Periodic reassessment before PPV
- Medical treatment
- **Management of VH:**
  - **Spontaneous resorbtion of VH is expected for 3–6 months**
  - ***Conservative—medical treatment:***

    Rest in bed
    Raising the head to 30–45°
    Binocular patching

- All these are meant to favor the sloping position of the blood and the sedimentation of the red cells with the partial clarification of the vitreous, allowing the examination of the fundus in the upper portion where the retinal tears are most frequently present.
  - ***Causal, etiological treatment***
  - ***Treatment by laser photocoagulation***

    Laser photocoagulation is indicated in CH in the presence of disc or diffuse retinal neovascularization to achieve peripheral retinal ablation in ischemic areas.
    Panretinal photocoagulation—significantly reduces the risk of long term VA decline.

  - **Laser photocoagulation does not clear the vitreous, but can prevent future episodes of VH and interrupt fibrovascular proliferation, preventing progression of retinal tractions and retinal detachment.**
  - ***Treatment by cryoapplications***
  - ***Treatment with intravitreal anti VEGFs***

    Induces regression of new vessels until laser photocoagulation is possible. *Intravitreal* antiVEGFs help rapid clearing of VH by inducing the resorption of new vessels (as early as 24 h after injection)

  - **Surgical treatment—PPV clarifies the vitreous and is performed between 6 weeks to 3 months if VH did not clear spontaneously.**

Treatment Indications According to the Casuse of VH

- For the risk of rebleeding—capillary protective, hemostatic
- Control and stabilizatin of arterial hypertension, diabetes
- Intraocular pressure control through eye drops and systemic therapy
- Enzymatic treatment was tried through intravitreal injections of hyaluronidaze in patients with vitreous hemorrhage and diabetes mellitus with beneficial effects.
- Patients with hypertension and diabetes were treated with antioxidant—histochrome which proved to be effective in recent vitreous hemorrhages in patients with nonproliferrative diabetic retinopathy.
- Retinal circumferential cryocoagulation may be a useful treatment in diabetic vitreous hemorrhage by favoring reabsorbtion and decreasing the vitrectomy rate.

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Chapter 19
Pupil

Magdalena Anițescu

Abstract **Photomotor response**—PMR **direct** is the miosis of the pupil of the illuminated eye and PMR **indirect,** consensual is miosis of the pupil in boths eyes illumination of one eye. PMR disruption by affecting the afferent pathway in relative afferent pupillary defect—RAPD—**Marcus Gunn pupil**. In severe retinal pathology with decrease in VA complet afferent pupillary defect is **amaurotic pupil**. PMR disruption by affecting the efferent pathway: sympathic damage—**Claude Bernard Horner syndrome** (ptosis, miosis, aparent, enophtalmia) and parasimpathetic damage in **cranial nerve III palsy** (mydriasis, cyclopegy, ptosis, paralitic strabismus, heteronymous diplopia) and **Adie tonic pupil** (the affected pupil in moderated dilated relative to the healthy pupil in medium illumination). **Argyll Robertson syndrome** in which the two pupils are small, and irregular, contract slowly, but strongly (punctiform in accomodation and convergence). PMR is absent but the convergence reflects is preserved. Is possible: **disorders of pupilary statics** (number, location, color, form), **motor pupilary disorders** (isocoria uni/bilateral, miosis unibilateral, midriasis uni/bilateral, paralytic spastic).

Keywords Photomotore response direct · Indirect (PMR) · Claude Bernard Horner syndrome · NC III palsy · Addie tonic pupil · Argyll Robertson syndrome · Static · Motor pupilary disorders

The pupil is a central opening, located at the level of the iris diaphragm, mobile, that allows the passage of light rays to the retina at the level of the macula in the foveola for the formation of the visual image.

The change in the size of the pupil under the action of light or darkness is produced by the contraction and relaxation of the iris dilator muscle (radial, sympathetic innervation), pupil dilator muscle and the iris sphincter muscle (circular, parasympathetic innervation), pupillary-constrictor muscle [1, 2].

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The two pupils are equal, symmetrical, round, black in color, medium in size, with a diameter that can increase in **mydriasis** or decrease in **miosis,** the miosis-mydriasis pupil play being permanent.

- **The constricting action of the parasympathetic nervous system is dominant.**

  Direct light into the two pupils produces bilateral pupillary constriction.

Photomotor Response—PMR

PMR occurs when one eye is illuminated and both pupils' contract [3].
PMR includes:

- **Direct PMR**—is the miosis (contraction) of the pupil of the illuminated eye
- **Indirect, consensual PMR** is miosis (contraction) of the pupil in both eyes upon illumination of one eye.

PMR includes:

- afferent path
- efferent pathway
  - parasympathetic to the pupillary sphincter muscle
  - sympathetic to the pupillary dilator muscle

PMR Disruption by Affecting the Afferent Pathway [4]

- **complete afferent pupillary defect—amaurotic pupil**
  - is produced by lesions of the homolateral optic nerve.
  - visual acuity (VA) is absent—f.p.l.
  - Consensual and direct PMR to light stimulation of the injured eye produces **amaurotic pupillary rigidity** in the affected eye with absent PMR, but with the preservation of consensual PMR in the fellow eye.
  - normal accommodation/convergence reflex
- **relative afferent pupillary defect—RAPD—Marcus Gunn pupil**
  - is produced by incomplete lesions of the ipsilateral optic nerve in severe retinal pathology with significant decrease in VA.
  - the two pupils are equal, but **upon illumination the pupil dilates (in 4 degrees), NOT miosis.**

    Type I—immediate pupillary dilation
    Type II—slow pupillary dilation
    Type III—initially normal pupil followed by slow dilation

Type IV–initially miosis, then mydriasis greater than in the fellow eye

- Etiologically: extensive retinal diseases, optic neuropathy, chiasmatic lesions, of the contralateral optic tract.
- Ipsilateral light stimulation generates diminished response in both eyes, contralateral stimulation–provides normal response in both eyes.

PMR Disruption by Affecting the Efferent Pathway (Table 19.1)

- sympathetic damage
  - Claude Bernard Horner syndrome
- parasympathetic damage
  - cranial nerve III palsy
  - Adie pupil

Wernicke Hemianoptic Reaction
- the absence of pupillary reaction to light when the half of the retina connected with the visual fibers related to the intracranial pathological process is illuminated.
- allows to differentiate lesions of the visual pathway up to the chiasm and anterior 2/3 of the bands from lesions of the posterior 1/3 of the optic bands, optic radiation, occipital cortex that do not cause pupillary reflex disorders.

PMR Disruption by Affecting the Efferent Pathway

Affecting the Sympathetic System

CLAUDE BERNARD HORNER'S SYNDROME THROUGH PARALYSIS OF THE SYMPATHETIC NERVOUS SYSTEM (SNS).

Clinically [5, 6]

- normal response to light and converging with normal bilateral PMR, delayed dilation when turning off the light
- small **ptosis** 1–2 mm by affecting the smooth fibers of the levator—Müller muscle with slight lifting of the lower eyelid.
- accentuated anisocoria in the dark that is produced by damage to the sympathetic fibers innervating the pupillary dilator.
- contraction of the pupil—**miosis** with the pupil smaller than in the healthy eye.
- **apparent enophthalmia**
- sometimes ipsilateral facial anhidrosis (when the lesion is anterior to the superior cervical ganglion)

Table 19.1 PMR disruption [5]

PMR		Syndrome	Pupil sizes	Pupil margins	PMR		Near response
					Direct	Consensual	
Afferent system		Amaurotic pupil	Mydriasis	–	Abolished	Abolished	N
		RAPD	N	**N**	Mydriasis	N	–
Efferent system	Parasympathetic	CN III palsy	Non-reactive high mydriasis	N	Absent	Absent	N
		Adie pupil	Mydriasis	Irregular	Slowly present	Slowly present	Healthy eye pupil slow reaction, tonic
	Sympathetic	Horner	Miosis	N	N, delay in dilation upon light out	–	Hyperactive accommodation

- hypochromic iris heterochromia (more in the congenital form)
- slow pupillary dilation
- hyperactive accommodation
- dilated conjunctival and facial vessels.
- ocular hypotony

Congenital Claude Bernard Horner's syndrome

Etiology
- obstetric brachial plexus injury
- obstetric carotid trauma (forceps)
- tumors: neuroblastoma, lymphoma

Acquired Claude Bernard Horner's syndrome

Causes
- I neuron damage in: tumoral, vascular brain pathology, syringomyelia and Wallenberg's lateral medulla syndrome.
- II neuron damage in low cervical and high thoracic injuries in: surgical trauma, tumors (Pancoast tumor)
- III neuron damage in: Claude Bernard Horner's syndrome, painful in internal carotid dissection, cavernous sinus tumors, nasopharyngeal tumors, orbital lesions, otitis media.

Horner's Syndrome in Children

- present at birth with heterochromia (benign)
- idiopathic
- after brachial plexus trauma (rare)
- neuroblastoma with invasion of the cervical and/or thoracic sympathetic chain

Affecting the Parasympathetic Nervous System: May Involve [7]

First neuron—PALSY OF CN III

Clinically
- active mydriasis, cycloplegia
- ptosis

- paralytic strabismus
- heteronymous diplopia
- relative dissociation of PMR and near reflex—pupil does NOT react to light but has normal near response.

Causes
- mesencephalic lesions with Parinaud syndrome where the pupils are moderately dilated and have no response to light.
- diabetes, hypertension, vasculitis
- myotonic dystrophy
- trauma, subdual, extradural hematoma with uncal herniation
- posterior communicating artery aneurysm at the junction with the internal carotid artery
- tumors

The Second Neuron—ADIE TONIC PUPIL

- it is produced by damage to the short ciliary nerves that innervate the pupillary sphincter and ciliary muscles.
- more common in women (70%) and in young men 20–40 years old
- initially unilateral, can become bilateral—4% per year.
- asymptomatic 20%

Symptoms
- blurred vision through paralysis of accommodation with difficulty when reading.
- photophobia to bright light
- pain in forehead when working implies the near vision, due to ciliary spasm.
- accommodation-induced astigmatism

Clinically
- abolished or diminished PMR
- slow, damaged accommodation
- **the affected pupil is moderately dilated relative to the healthy pupil in medium illumination.**
- slow constriction in convergence after slow redilatation.
- in convergence, the abnormally large pupil becomes the smallest—the inversion of anisometropia.
- vermicular movements of the iris in the sector
- hyposensitivity of the cornea
- the Adie pupil is a tonic pupil that dilates very slowly.

Causes
- lesions of the ciliary ganglia: HSV infection, inflammation (sarcoidosis), trauma, orbital, ocular surgery

The Near Pupillary Reflex: Sinkinesis

It is located in the superior peristriate cortex area 19 and the posterior calcarine sulcus. When viewing a near object, the following occurs at the same time:

- **convergence reflex**
- **accommodation of the lens**
- **miosis**

The cortical field of the near pupillary reflex is located more anteriorly than the PMR, which explains the dissociation of light/near pupillary reactions in the Argyll-Robertson pupil.

ARGYLL ROBERTSON SYNDROME in which the two pupils are small and irregular, contract slowly but strongly (punctiform) in accommodation and convergence [8].

Clinically

- **PMR is absent, but the convergence reflex is preserved**
- bilateral miosis, generally asymmetric
- pupils—small, irregular, slightly reactive to light, reactive to accommodation and convergence
  - near/far dissociation
  - difficult dilation

Causes: neurosyphilis (most common) diabetes, tumors, encephalitis.

Light/Near Dissociation [9]

- high VA drop—retinal, optic nerve disorders up to chiasm
- *panretinal photocoagulation* (PRP), *cryocoagulation*—lesions of the posterior short ciliary nerves
- Adie pupil—damage to the ciliary ganglion
- aberrant regeneration of III cranial nerve III—peripheral neuropathy

Dissociation of Near/Far Pupillary Reaction

- PMR is diminished or absent, with preservation of the convergence reflex:
  - unilateral: RAPD, Adie pupil, aberrant regeneration of CN III
  - bilateral: neurosyphilis, DM, Parinaud syndrome, encephalitis, alcoholism

Psychosensory reflex—pupil dilation in the presence of psychic sensory stimuli.

- The normal pupil has a diameter of 2–4 mm, a diameter that can change under the action of light/dark or under the action of medicinal substances.
  - **miotic pupil** is produced by parasympathomimetic substances: pilocarpine, ezerin
  - **the mydriatic pupil** is produced by:

    parasympatholytics: atropine 1%, homatropine 1%, tropicamide (mydrum)

  - mydriasis produced by atropine increases after cocaine instillation (excites sympathetic fibers and allows PMR to persist)
  - sympathomimetics: adrenaline

Pupillary Reflexes Producing Miosis

- direct and consensual photomotor reflex (to light)
- the near response
- orbicularis-pupillary reflex (trigeminal)
- attention reflex (Haab)

Pupillary Reflexes Producing Mydriasis

- reflex to darkness
- sensitive reflexes to pain, auditory, tactile, gustatory stimuli
- psychomotor reflex—fear, emotion

Disorders of Pupillary Statics [2]

Number—multiple pupils, polycoria.

Location—eccentric pupil—correctopia (inflammation, iridociliary, trauma, surgical interventions)

Color

- normal, black
- gray in cataract, reddish in vitreous hemorrhages, yellowish in glioma, panophthalmia, greenish in glaucoma, white pupil (leucocoria) in retinoblastoma, retinopathy of prematurity, endophthalmitis
- Abnormalities of form
- coloboma (inferonasal)
- corectopia
- aniridia
- Anomalies of the edges of the pupil: irregular due to synechiae, in iridocyclitis, tumors, trauma

Motor Pupillary Disorders [2, 10]

Isocoria

- the two pupils are equal, symmetrical or there is a difference of 0.5–1 mm, the two pupils may be in:
- miosis—pupils less than 2 mm
- mydriasis—pupils larger than 4 mm
- isocoria with normal pupil sizes; is present in **Relative Afferent Pupillary Defect—Marcus Gunn Pupil—RAPD**
- upon illumination, pupil dilation occurs instead of miosis.

Unilateral Miosis

- Ocular
- congenital in aplasia of the dilator muscle
- drug-induced—parasymptomimetics (pilocarpine, ezerin)
- reflex in: keratitis, iridocyclitis, corneal foreign bodies, ocular contusion
- Senile
- Paralytic in Horner's syndrome (ptosis, miosis, enophthalmia)

Bilateral Miosis

- Central cause: stroke, encephalitis, meningitis, opium, nicotine intoxication, severe hypoxia, uremic coma
- Tetanus
- Argyll Robertson pupil—the pupil reacts poorly or not at all to light, but is normal in convergence.

Normal mydriasis: children, myopes, light colored iris

Unilateral Mydriasis

- Ocular
- parasympatholytic eye drops (atropine), sympathomimetics (adrenaline, cocaine)
- congenital anomalies
- acute glaucoma, absolute glaucoma
- old CRAO
- AION
- RD
- optic atrophy
- Systemic: migraine, meningitis, meningoencephalitis, HZV

Bilateral mydriasis in severe comatose states in:

- tumors, brain trauma, meningeal hemorrhage, stroke, epilepsy, neuropsychiatric conditions, poisoning (botulism, mushrooms, belladonna), diabetes
- pharmacological mydriasis after tropicamide, atropine, cyclogyl

Paralytic mydriasis in CN III palsy in trauma, brain tumors, stroke, meningeal hemorrhage, aneurysm.

Spastic mydriasis in compressions of the cervical cord, cervical sympathetic nerve in: tumors, trauma, thoracic conditions, mediastinal tumors

Eye drops test—aims to highlight the pupillary response to administered substances in order to specify the pathological pupil and whether the sympathetic or parasympathetic system is affected [5].

Substances used: cocaine 2%, homatropine 0.5%, adrenaline 1%, pilocarpine 0.1%.

A drop of 2% cocaine (sympathomimetic action) is administered indirectly to the eye with the **larger pupil**

- the pupil dilates only if the sympathetic postganglionic fibers are intact.
- Result
  - normal pupil—dilates moderately
  - if the mydriasis occurs by sympathetic excitation, cocaine has no effect
  - if the mydriasis occurs by parasympathetic excitation, it becomes maximal
- a drop of **cocaine** is administered **to the eye with the smaller pupil**

possible result:

- normal pupil—slight mydriasis
- without pupillary effect there is parasympathetic spasm or sympathetic paralysis with paralytic miosis
  - one **drop of homatropine** 0.5% (adrenergic blocker) is administered.
  - possible result:

    mydriasis occurs in spastic miosis.
    in miosis by sympathetic paralysis—null pupillary response**The abnormal pupil is dilated.**

- ***no tonic contraction***
  - ***CN III palsy (ptosis, mydriasis, cycloplegia, divergent strabismus)***
  - Drug-induced mydriasis—atropine
  - posttraumatic, neoplasm
- ***with tonic contraction***
  - **Adie pupil—**the affected pupil is moderately dilated compared to the healthy pupil in high lighting, the tonically dilated pupil reacts minimally to light and slowly in convergence.
  - Non-reactive bilateral mydriasis (can be an emergency) in: botulism, Parinaud syndrome, brainstem occlusion, drug-induced mydriasis.**The abnormal pupil is miotic.**
- ***Horner's syndrome*** with: ptosis, miosis, enophthalmia.

Anisocoria

Anisocoria is the size inequality between the two pupils—anisocoria can be intermittent, asymptomatic, more common in the elderly [11].

Anisocoria—the two pupils are different sizes.

Anisocoria is produced by an imbalance between sympathetic and parasympathetic efferent pupillary pathways.

Anisocoria is present in: Horner's syndrome, Adie pupil, CN IV palsy, Argyll Robertson pupil, Hutchinson pupil, iriens synechiae, drug-induced mydriasis.

The emergency in anisocoria is given by the painful Horner's syndrome within carotid dissection and painful CN III palsy with mydriasis in ruptured posterior communicating artery aneurysm.

PHYSIOLOGICAL ANISOCORIA is the size difference < 1 mm in 20% of cases, asymptomatic.

Anisocoria Grows in the Dark: The Small Pupil Is Abnormal

in the light the two pupils are identical

in the dark the pathological pupil does NOT dilate (miosis)

Claude Bernard Horner's syndrome—*oculosympathetic* paresis

Cocaine Drop Testing [12]

- instill 2 drops of 4–10% cocaine into both eyes
- after 45′–60′
  - normal pupil—dilated
  - Horner pupil—medium, small dilation
  - anisocoria increases

Apraclonidine (Iopidine) Testing [13]

- instill 2 drops of 0.5–1% in both eyes
- after 30–45′normal pupil is undilated
  - Horner pupil—dilated
  - anisocoria reverses, widening of the palpebral fissure

Hydroxyamphetamine Test—PAREDRINE

- 45′ after the instillation of 2 drops:
- normal pupil—dilates
- postganglionic Horner pupil—slightly dilated
- preganglionic Horner pupil—first and second neuron—dilated Horner pupil
- The cocaine drop test can interfere with hydroamphetamine, so it is recommended to perform the two tests 72 h apart.

- **Painful Horner's syndrome—**in internal carotid artery dissection and CN III paralysis in ruptured posterior communicating artery aneurysm (neurosurgical emergencies).
- **"Tadpole" pupil**—intermittently, the pupil of one eye may become irregular, distorted, with sector pupillary dilations for 1–2 min due to episodic sympathetic irritation (possible cervicothoracic spinal cord trauma.
- **Argyll Robertson pupil**—rarely, with bilateral asymmetric miosis with small irregular pupils, poorly reactive to light, but reactive in accommodation and convergence
- near/far dissociation
- difficult dilation

Anisocoria Increases in Light

- in obscurity the two pupils are identical
- the abnormal pupil is wider
- to light, the pathological pupil does NOT lead to miosis, it does not constrict, it remains in mydriasis
- it is due to damage to the postganglionic innervation of the pupillary sphincter and the ciliary muscle.
- causes of mydriasis:
  - at ocular level: posterior synechiae, angle-closure glaucoma, trauma, capsular pseudoexfoliation, mydriatics, parasympatholytics (atropine, homatropine, cyclopentolate, mydrum) or sympathomimetics (adrenaline, phenylephrine, bronchodilators)
- Pilocarpine 0.1% test
- one drop of pilocarpine of 0.125% in both eyes
  - if there is no response, apply pilocarpine 1–2% in both eyes

    the normal pupil contracts
    the dilated pupil contracts a little, or does NOT contract—pharmacological mydriasis is confirmed

CN III palsy, rarely in ophthalmoplegic migraine in young people.

Adie tonic pupil—with unilateral, regular, isolated, painless mydriasis, with onset of accommodation paralysis that affects reading

- systemically—reduction of osteotendinous reflexes
- symptoms—photophobia, blurred near vision, headache
- ocularly:
  - the affected pupil is moderately dilated relative to the healthy pupil in medium illumination

the tonic pupil, with absent constriction, dilates very slowly

- the tonically dilated pupil reacts minimally to light and is slowly in convergence
- in convergence, the inversion of anisometropia, the abnormally large pupil, becomes smaller

  abolished or reduced PMR
  vermiform pupillary movements

- denervation hypersensitivity after instillation of diluted pilocarpine 0.125%

- Pilocarpine 0.125% pharmacodynamic test
  - the normal pupil is insensitive to diluted pilocarpine
  - the Adie pupil fixes in significant miosis

Disorders of Pupillary Dynamics

Regarding the pupil, the diameter changes depending on the luminous flux entering the eye, controlled by antagonistic forces of the parasympathetically innervated constrictor iris sphincter muscle and the sympathetically innervated (radially) iris dilator muscle [10].

The functioning of the pupil is reflex and is achieved by:

- **The direct and consensual photomotor reflex**—which consists of miosis on both eyes when one eye is illuminated
- **Miosis/accommodation/convergence pupillary reflex in near vision**

Pupillary dynamics disorder is related to:

- PMR disruption
- Argyll Robertson pupil

Disruption of PMR

- afferent deficit
- relative afferent pupillary deficit—RAPD
- complete afferent pupillary deficiency—amaurotic pupil
- efferent deficit
  - affecting the sympathetic nervous system
  - Claude Bernard Horner's syndrome
  - parasympathetic nervous system impairment
  - CN III palsy
  - Adie tonic pupil

Argyll Robertson pupil—the two pupils are small, irregular, contract slowly but are very (punctiform) in accommodation and convergence [8].

It is produced by damaging the reflex arc at the level of the Edinger-Westphal nucleus.

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Chapter 20
Optic Nerve Pathology

Marieta Dumitrache

Abstract **Papillary stasis** is the non inflammatory papillary edema of the head, ON produced by intracranial pressure rise. The causes of stasis are: posterior cerebral fossa tumor, meningitis, encephalitis, cavernous sinus, thrombosis. Treatment is neurosurgical immediate. **Pappillytis** infectious inflammatory, in which the optic disc is affected with present edema. **Retrobulbar nevritis** RBN in which the lesion is located along ON with papillary edema present in 35%. RBN **is present** in demyelinating affection in SM. **Ischemic optic neuropathy** is anterior, after etiology this is arteritic Horton disease and nonarteritic neuropathy. **Immune mediate inflammatory optic neuropathy** in: Behcet, Voght Koyanagi Harada, **Infectious optic neuropathy** may be associated with bacterial infection (TBC, Whipple, Lyme), viral disease (CMV, ARN, PORN), in systemic disease sarcoidosis, Wegener. **Toxic, metabolic, nutritional, optic, neuropathy. Optic atrophy** is an irreversible degeneration of the pregeniculate fascicole of the ON with VA decrease major.

Keywords Papillary stasis · Papillitis · Retrobulbar nevritis · Ischemic optic neuropathy · Inflammatory infectious · Optic · Metabolic optic neuropathy · Optic atrophy

- Optic neuropathies are diseases of the ganglionic fibers of the ON that start from the optic papilla till the optic chiasm.
- The stop of axoplasmic flow in optic neuropathies may occur through multiple etiopathogenic mechanisms:
  - Inheritance through mitochondrial deficiency
  - Infectious inflammatory

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- Demyelination
- Metabolic by decreasing blood flow
- CRF pressure rise through direct compression
- Food shortage
- Direct toxic effect (drugs) or metabolic deficit
- Post-traumatic through: avulsion, sectioning of the ON, compression, ischemia.**Optic nerve pathology includes:**

Anterior optic neuropathies with papillary edema

- Generated by the damage to the ON from the papilla level till the entrance of the central vessels of the retina in the papilla 10–12 mm through various mechanisms: infectious inflammatory, ischemic, CRF pressure rise, toxic, post-traumatic

Optic neuropathies with papillary edema are [1, 2]:

- **Papillary stasis—**mechanical edema of the ON head in ICHT
- **Papillitis** or **juxtabulbar optic neuritis—**the infectious inflammatory process located at the papilla level (head of the ON) is accompanied by light papillary edema prominently visible +2+4 SPH and by a high VA decrease
- **NRB—**papillary edema in 35%, the rest, normal eyesore with ON damage after exiting the papilla
- **AION-A, AION-N—**arteritic ischemic optic neuropathy (A) or non-arteritic (N)
- **Cerebral pseudotumor—**benign ICHT
- **Papillary pseudoedema** in long sightedness, drusen
- **Compressive optic neuropathy—**anterior form
- **Infiltrative optic neuropathy—**anterior form

Posterior optic neuropathies [1, 2]

- **NRB—**except for the multiple sclerosis of the infectious inflammatory process, toxic, degenerative of the ON from the papilla (optic disc) till the crossing in the chiasma
- **NRB—**toxic, metabolic, nutritional
- **Compressive optic neuropathy—**posterior form
- **Infiltrative optic neuropathy—**posterior form
- **Hereditary optic neuropathies: Leber, Kjer, Behr, Wolfram**
- **Optic atrophy**

Anterior Optic Neuropathies with Papillary Edema

Papillary Stasis

- Papillary stasis is the non-inflammatory papillary edema of the head of the ON produced by intracranial pressure rise [3].
- Stasis papillary edema is bigger than +4D; VA is normal or slightly lowered, at first the VA is decreased in 30–45 days with the installation of optic atrophy.
- The causes of papillary stasis are multiple:

- Posterior cerebral fossa tumors, which obstruate the Sylvius waterduct, cerebellum tumors, etc.
- Meningitis, encephalitis, cerebral abscess, intracranial hemorrhage, subarachnoid hemorrhage
- Cavernous sinus thrombosis
- Trauma
- AHT, nephritis, blood dyscrasias

- **General signs** [1, 4]
  - **Cefaleea**

    Present in 80–90% of cases
    Appears early, is progressive, more intense upon awakening in the morning, related to the ICP rise during the night and partially lowered after vomiting
    Diminish or even disappears with the papillary edema decrease and the installation of the optic atrophy

  - **Nausea and vomiting—**appear late if the ICHT is severe
  - **Vomiting**

    In the morning, with a jet, without nausea, without effort, with the easing of the cefaleea after vomiting
    Characteristic for children with IV ventricle tumors where they appear early

  - **Mental disorders**

    Can be more frequent than vomiting
    Behaviour disorders: irritability, aggressivity, intermittent sleepiness alternated with stupor (sign of cerebral hernia).

  - **Tumoral locating signs**

    VI paresis, meningeal irritation signs, comitial seizures, vertigo, nystagmus
    In severe forms: loss of consciousness, coma, mydriasis, death.
    Aggravating of the ICHT is done when the patient becomes apathetic, sleepy, confused +- pyramidal syndrome, vegetative disorders, cranial nerve damage.
    Mental disorders predominate in the elderly, paresis, convulsive seizures, late fundus changes.
    In the small child, infant—vomiting, oculomotor paresis, bulging of the fontanel, hydrocephalus, “looking upwards”
    Ocular signs

    Visual symptoms, absent at first but they can occur

    Transitory loss of VA when the patient rises from the horizontal for a few seconds
    Phosphenes, visual eclipses

VA drops suddenly and importantly when the optic atrophy installs

VF with variable amputations depending on the tumor location, with enlarging of the blind spot, at first, lower VF amputation, frequently parallel with the decrease of VA.
Diplopia, occasional paralysis of the VI cranial nerve
DPAR
Eyesore—**Papillary stasis edema is an oftalmo-neurological emergency**

The edema is bilateral, asymmetric, progressive, with VA normal at the start; blind spot enlarging
Stage I

Normal-VA
Blurred papillary contour with peridiscal edema, with nasal superior start, inferior
Conserved optic cup (differential diagnosis with pseudoedema and discal drusen)
Small flaming hemorrhages peripapillary
Spontaneous venous pulsations, they disappear if the ICHT rises, artery/vein ratio 4/2
Peripapillary retinal folds

Stage II

Prominent papillary edema +6+8D
Indistinguishable optic cup
Blurred papillar margins with prominent nasal margin

Stage III florid stasis

Prominent papilla through edema 1 mm—3 diopter—visible with +6+8D and with relatively good VA
Differential diagnosis with papillitis where the papillar edema is seen with +2+3D sf. and very low VA
Indistinguishable optic cup
Peripapillary radiar hemorrhages and cottony nodules give the papilla the aspect of a “chrysanthemum flower”
Concentric or radiar retinal folds (Paton lines) +- choroidal

Stage IV

Severe papillary edema
Obliterated optic cup
Reduction of hyperemia
Total segmental obstruction of blood vessels

Stage V

Poststasis optic atrophy with atrophic optic papilla, cretaceous white with slightly raised margins, thin vessels +- bottled up.

Foster Kennedy syndrome—papillary edema at one eye and optic atrophy at the other

Optic atrophy is produced through direct tumoral pressure and the papillary edema on the other eye through ICH
More frequently through frontal tumors (pathognomonic for olfactory meningioma), sphenoidal wing meningioma, AION from Horton disease.

Differential diagnosis of the stasis edema is made with (Table 20.1):

Papillary pseudoedema from the optic Dursen and long sightedness
Cerebral pseudotumors (idiopathic ICHT)
Other papillary edema causes

ON head tumors (astrocytic hamartroma, glioma)
Compressive orbital diseases

Table 20.1 Differential diagnosis of the papillary stasis

	Stasis	Pseudoedema	Papillitis	BRN	AION
Uni/ bilateral	– Bilateral – Asymmetric	Uni/bilateral	Unilateral	Uni/bilateral	– Uni/risk bilateral
VA decrease	– Transitory VA decrease – Initial normal VA – Late high VA decrease	– Optic correction	– High VA decrease	– High VA decrease with return to N – Dyschromatopia red/green	Acute visual deficit
VF	Hemianoptic	– Normal	– Blind spot enlargement – Arciform deficit	– Central big scotoma at red/ green color	– VF deficit which respects the horizontal median
FO	– Very prominent papillary edema, visible with +6+8D – “Chrysanthemum flower” aspect – Optic atrophy	– Small red papilla with pale margins	– Slightly prominent papillary edema, visible with +2+4 sf.	– 70% normal – 35% papillary edema	– Pale edema of the papilla with peripapillar hemorrhages
Pupil	– Normal	– Normal	– RAPD	– RAPD	– RAPD
Prognosis	Fast diagnosis, otherwise optic atrophy	–	Good under treatment	Reserved in MS	– Reserved-1/3 relapse

Diabetical opticopathy
AION
Papillitis where the VA is much lowered and the prominence of the papilla is reduced (+2+4D)
Malignant AHT
ON infiltrations in sarcoidosis, TBC, leukemia, metastases

Differential Diagnosis of the Papillary Stasis (Table 20.1)

- Treatment [5, 6]
  - Fast identification of the ICHT cause and causal treatment
  - Neurosurgical treatment

    Immediate extirpation of the tumor (if possible)
    Lumboperitoneal shunt, ventriculoperitoneal with or without valve which prevents VA decrease, reduces headaches and edema
    ON sheath fenestration
    Venous sinus stent

Cerebral Pseudotumor: Benign Intracranial Hypertension

- Condition present at 20–45 year old women, obese with fast body mass growth, after treatments with: oral contraceptives (through hypercoagulability and dural sinus thrombosis), vitamin A, nalidixic acid, lithium, steroids, extended surgery of the neck, ears, chronic pulmonary diseases [7].
- Symptoms [8]
  - Asymptomatic
  - Transitory decrease following VA and contrast sensibility
  - VF defects
  - Diplopia
  - Pulsating tinnitus
  - Nausea, vomiting
  - Dizziness
- Clinical
  - Bilateral papillary edema
  - Possible CN VI paresis
- Systemic associations: Adisson, chronic pulmonary diseases, dural sinus thrombosis.
- Positive diagnosis through exclusion:

  - ICHT signs
  - CRF pressure increase >250 mm H_2O at obese people, >200 mm H_2O at non-obese people, but normal content
  - Normal neurological exam excepting VIth nerve paresis and papillary edema
- Medical treatment [7]
  - Acetazolamide 500 mg × 2 × 4/day
  - Furosemide in 4 shots
  - Oral steroids 60–80 mg/day depending
  - NSAI
- Surgical treatment if the decrease in vision continues through lumbago peritoneal shunt, ON sheath fenestration.
- Repeated lumbar points assure 25% remission.

Papillary Pseudoedema

- The papillary edema that appears in:
  - Small hyperemic papillar disc, prominent depending on the long sightedness value
  - Optic disc drusen [9]
  - Hyaline material (drusen) located in the optic disc
  - Small optic disc, red, prominent with irregular estompated margins, with absent optic cup, with peripapillary pigment epithelium defect
  - There are no hemorrhages, exudates, arteries are normal
  - VF—enlarging of the "blind spot"

Optic Neuropathies (Optic Neuritis)

- Primary inflammations of the ON which consist of two clinical forms
  - **Papillitis**—in which the optic disc is affected (papilla), which presents edema
  - **Retrobulbar nevritis—RBN**—in which the lesion is located along the ON (from the papilla till the chiasm), and the optic disc is normal or can present papillary edema (35%) (Table 20.2).
- Anterior optic neuropathies—PAPILLITIS and posterior—RETROBULBAR OPTIC NEVRITIS have common etiology.
  - Anterior optic neuropathies are predominant infectious/inflammatory, RBN having demyelinating, toxic causes

    Infectious causes

Table 20.2 Causes of optic nevritis

Bacterial infections	Viral infections	Fungal infections	Parasites
– Beta hemolytic streptococcus – Mycobacterium tuberculosis – Meningococcus – Mycoplasma pneumonia – Brucella – Salmonella, Shigella – Sifilis – Borrelia Burgdorferi – Leptospira – Bartonella henselae	– HSV 1,2 – HZV, chicken pox – CMV – Coxsakie – Adenovirus – Measles – B hepatitis (vaccination)	– Candida – *Aspergillus* – Cryptococcus – Coccidiosis – Mucor	– Toxoplasm – Toxocar – Histoplasm – Onchocerciasis

Local intraocular infections (uveitis, scleritis) intraorbitar, rhinosinusal **(ethmoidal sinusitis), meningeal (TBC, sifilis, meningitis)**
General infections: bacterial, viral, parasitary, mycotic

Focal causes: sinusitis, dental affections, tonsillar
Inflammatory causes

Sarcoidosis
Behcet
Vogt-Koyanagi-Harada
Systemic vasculitis: LES, Wegener granulomatosis, giant cells arteritis

Anterior Juxtabulbar Neuropathy: Papillitis

- Papillitis is the inflammatory process of the anterior portion of the ON
- Symptoms [10]
  - **Sudden drop in VA,** the level of VA decreases depends on the papillo-macular beam affection.

    VA decrease has a fast evolution in the first days, stabilises (days, weeks) and is followed by tempering (even return to normal).

  - **Visual field**

    "blind spot" enlargement with photometric disharmony
    Central scotoma, paracentral
    Peripheral narrowings (rare)

  - **Chromatic sense** progressive red/green, yellow/blue dyschromatopsia.
  - **Ophthalmoscopic ocular signs**

    Congeste papilla, blurred edges, asymmetric
    Papillo-peripapillary edema visible with +2+4D, less prominent than the stasis edema, but with profoundly lower VA
    Peripapillary exudate and hemorrhage

Dilated veins, sinous

– Evolution

Acute phase, lasts 2–3 weeks with papillary edema +2+4 and high VA decrease
Regression phase, slower evolution, 1–2 months with reduction till the clinical signs disappear:

Favorable evolution with recovery (ad integrum restitution)
Unfavorable evolution with optic atrophy and VA decrease

– Differential diagnosis

Papillary stasis where the edema is bilateral, VA is normal or slightly lowered at the beginning and papillary edema is very big (+8+10D).
Anterior optic ischemic neuropathy where the VA drops suddenly, the edema is white ischemic and the patient older.
Retinal vascular damage: OACR, TVCR.

– Treatment

Cleaning up the outbreaks of infection
Treatment of the causal affections: NSAI, SAI—Prednisone 1 mg/kg/day, antibiotics at need.

Neuroretinitis

- Inflammatory edema of the papilla which extends to the nearby retina.
- The inflammation of the ON associated with the inflammation of the retina and choroid
- Clinical [11]
  - Papillary edema with or without hemorrhage which extends to the juxtabulbar retina, which appears almost at the same time or before the maculopathy
  - Maculopathy with edema and perimacular exudate in the shape of a star
  - The macular star progresses, evolves 7–10 days, reduces slowly after 6–12 months, papillary edema reduces
  - Juxtapapillary edema with variable extension with grey retina
  - Extended papillary edema can be warranted by optic atrophy
  - Vitritis
  - Cellular infiltrate in the AC
  - Chorioretinal inflammatory lesions
- Ethiological, neuroretinitis is of infectious cause
  - Bacterial infections

Secondary syphilis, tertiary syphilis

Borelia burgdoferi
Bartonela henselae

– Viral infections

HSV, HZV, CMV
Influenzae
Enteroviruses
Coxsackie
Measles, rubella

– Fungus
– Parasites

• Treatment

– Causal: antibiotics, antivirals, antimycotic, antiparasitary

Uveopapillitis

• An association between uveitis and papillitis, distinguishing two forms:

– Anterior form

Papillitis associated with a subacute or chronic iridocyclitis characterised by:

Plastic iritis, exudative or nodular
Important VA decrease
Central scotoma or fascicular deficit
Slightly prominent papillar-retinian edema which extends to the macula
Dilated veins no hemorrhages

Etiology: TBC, sympatic oftalmy, viral diseases

– Posterior form

Papillitis associated with choroidian, retinian or vitrian inflammatory signs
In case of vitrian touch, the transparency is variably decreased and so the ability of examining the papilla.

Neuropapillitis

• Inflammation of the juxtabulbar segment of the optic nerve is associated with the inflammation of the intracranial optic nerve, associated with a meningo-encephalic inflammation.

Uveomeningopapillitis

- Infectious process, frequently viral which interests simultaneously the uvea, optic nerve, meninges and the inner ear.
- Presents uveal signs, meningeal, encephalitic, cutaneous, neurological
- Can be presented in: sympathetic ophthalmia, Vogt-Koyanagi-Harada syndrome (undetermined uveomeningeal syndrome)

Ischemic Optic Neuropathy—ION

- After the location of the ischemy, ION can be:
  - **ANTERIOR—AION—**which affects the head of the ON and decrease of the VA is accompanied by ON head edema of the papilla

    After etiology AION is:

    Artheritic AION—A-AION—vasculitis with giant cells—Horton disease
    Non-artheritic AION—N-AION—secondary to the short posterior ciliar arteries obstruction, idiopathic or athero-sclerotic
  - **POSTERIOR—PION** in which the ischemia affects the retrobulbar segment of the ON and the papillary edema is absent

Anterior Ischemic Optic Neuropathy

Artheritic AION—A-AION

A-AION results from the ischemic involution of the anterior segment of the ON, generated by the short posterior ciliar arthery occlusion [12].

- Severe optic neuropathy (rare) at people over 55.
- The most frequent is **ocular manifestation in the giant cells (GCA), Horton disease,** but can be present also in other vasculitis: nodular periarteritis, Wegener granulomatosis, Churg Strauss syndrome, SEL
- Initially unilateral, can become bilateral (in hours, days).
  - Severity of A-AION is tied to the binding character of the disease, with definitive sight loss on the initially affected eye and possible fast bilateralisation [13].
- **Giant cells artheritis—GCA** is a granular necrotic bilateral vasculitis with unknown ethiology which affects mainly the small cliber artheries with the origin in the aortic arch: temporal artery, ophthalmic artery, short posterior ciliar artery, proximal segment of the vertebral arteries [14]

  - In GCA is produced a thrombotic occlusion of the short posterior ciliar arteries, secondary ischemy of the anterior segment of the ON that generates A-AION is the consequence of the occlusion
  - 21% of the patients with GCA do NOT have symptoms and systemic signs
  - Frequently, patients with A-AION present amaurosis fugacea or transitory diplopia (1/3 of cases) without a connection with sight decrease
  - In GCA are produced systemic neurological, cardiovascular but also ocular lesions through the damage of the superficial temporal artery, oftalmic artery, occipital, vertebral, sometimes aorta, subclavian or the carotid
  - GCA affects patients over 50 years old, more frequently Caucasians
  - GCA is a fast progressing affection with irreversible blindness [15].

- Horton disease suspicion [16]
  - Patient over 50 years old, the freuence of the disease grows with every decade of life (very rare at young people)
  - Temporal cephaleea
  - Before the manifestations of the AION

    Transient diplopia
    Visual disorders: transitory amaurosis fugacea
    Ocular pain
    OF—optic disc with pale chalky edema; retinal arterial occlusion; choroidal ischemia
    Increased HSS, PRC

- Horton disease signs [17]
  - Overall condition alteration
  - Fever
  - Anorexia
  - Hypersensitivity of the scalp
  - Myalgia
  - Indurated temporal arteries, nonpulsatile, painful at touch
  - Intermittent jaw claudication
  - Increased HSS, PRC
  - Signs of rhizomelic polyarthritis

- Ocular symptoms [18]
  - Fast unilateral VA decrease (days, hours), severe (l.p.f.) together with pain, preceded by FA a few weeks prior, as in the carotid diseases
  - Diplopia
  - RAPD
  - VF: inferior chronic deficit, centrocecal scotomas, generalised deficit.

- Ophthalmoscopic ocular signs [19]

  - Differentiated edematous optic disc with papillary chalky white extended edema, which reduces in 4–8 weeks and can be followed by optic atrophy.

    When the optic disc is edematiated, the optic cup is not distinguishable
    The optic disc area is significantly smaller than normal
    Rarely, the infarction can be located retrobulbar without papillary edema with PION

  - Pale peripapillary ring
  - "In flame" hemorrhage
  - Cotone exudates can sometimes be precocious
  - Difuse choroid atrophy around the optic disc
  - Choroid ischemia or central retinal artery obstruction or of a branch, which accentuates the loss of sight
  - The congener eye papilla can have a physiologically enlarged cup (suggestive for A-AION)
  - **In A-AION is necessary to evaluate the real dimensions of the optic disc including: perimeter, optic cup, neuroretinal ring through photos of the optic disc** [20] (Table 20.3)

- Pupillary modification with anisocoria, with the pupil in a reflexive mydiasis if perception, light projection is absent
- Local signs:

  - Induration of the temporal region with decrease or absence of the pulse in the temporal artery
  - Scalp necrosis

- Systemic signs and symptoms in AION

  - Can be present for days or years, before or together with visual symptoms

Table 20.3 Papillary edema differential diagnosis

	Stasis	Optic nevritis	ION
Visual symptoms	VA initially N	VA decreases fast	VA variable, low
Uni/bilateral	Bilateral	Unilateral, bilateral rare	Unilateral, bilateral risk
OF	– Very prominent papillary edema +6+8D – Hemorrhages, peripapillary exudates	Papillitis—papillary edema +2+4D, hemorrhages RBN—normal OF—30% papillary edema	Pale papilla edema Peripapillary hemorrhages
Pupil	Normal	Marcus Gunn +	Marcus Gunn +
Visual prognosis	Good, if the diagnosis is fast	Possible recovery, even full	Reserved Possible affection of both eyes
Other signs	Cephaleea, nausea, vomiting	Pain at the mobilisation of the eyes	Horton—cephaleea, TMA pain, high HSS

Rheumatic polymyalgia with painful affection of the proxima muscles, movement limitation, arthralgia
Cephalalgia
Sensitive scalp with cutaneous hyperesthesia
Maxillary claudication when talking or chewing

- **Cephalalgia and maxillary claudication are the most frequent symptoms**
- **The presence of maxillary claudication is a productive factor for sight loss risk**

Cachexia
Pallor
Anorexia
Confusion, dementia
Sleepiness, tinnitus, vertigo, facial pain, periorbital edema

- Lab exam:
  - HSS

    High in GCA >90 mm/h
    High at older people unspecific, in average the increase is till 50 mm/h

  - PRC increased >45 mg/dL

    High increase of the HSS >50 mm/h associated with PRC increase is specific till 95% for GCA diagnosis

  - Normochromic anemia
  - Leukocytosis
  - Thrombocytosis associated with increased HSS and PRC that allow differential diagnosis with A-AION
- OCT
  - Highlights the thickness of the LFNR
  - Before and after treatment, periodically
- Fluorescein, indocianin angio (FAG)
  - FAG has a relative sensitivity and specificity for GCA, but it is useful for confirming the positive diagnosis, associating the clinical context ocular and systemic manifested with sight loss at old people.
- Superficial temporal artery ultrasonography before the biopsy shows the inflammation of the vascular wall through the highlight of the hypoecogene concentrical ring, "halo sign"
- Colored Doppler shows the abnormal oftalmic artery, RCA, short posterior ciliary arteries and in the temporal artery with hypoecho in the edematous vascular wall
- MRI—necessary for differential diagnosis with

  - A-AION
  - PION
  - Other optic neuropathies—inflammatory, infiltrative

- Temporal artery biopsy
  - It is gold standard for positive diagnosis confirmation for GCA and it is necessary for differential diagnosis with other granulous vasculitis: Wegener, nodous polyarteritis, Bechet
  - Sets the diagnosis for Horton disease highlighting the subacute inflammatory panarteritis at old people (frequency peak 70 years) with segmentary and plurifocal topography, predominating in the cephalic segment, essential on the external carotid branches, predominating in the cephalic sector, essential on the external carotid branches and in particular the superficial temporal artery.

- Complications
  - Ocular

    Decrease/loss of sight at one or both eyes
    RCA occlusion or branch, oftalmic artery
    Anterior segment ischemia
    Choroidal infarction
    Transitory monocular cecity
    Transitory diplopia

  - Major neurological complications

    VCA
    Cranial nerve palsy (most frequent VI)
    Meningoradiculitis

  - Vascular complications

    Dissecting aneurism or ruptured aorta—15%
    Aortitis
    Aortic valve insufficiency

  - Complications of cortisone treatment

    Fractures
    Digestive hemorrhage
    AHT
    Psychosis
    Hyperglycaemia

  - Immunosuppressive treatment complications

    Aplastic anemia
    Pancytopeny
    Pancreatitis at azatioprin

- Positive diagnosis [21]
- After Hayreh—A-AION is confirmed through:
  - Histologic exam
  - Presence of symptoms and general signs
  - Ophthalmological signs
  - Decrease in VA—100%
  - Transitory amaurosis fugacea—30%
  - Diplopia—10%
  - Ocular pain—5%
  - Ischemic ophthalmological lesions

    RCAO—4%
    Cilioretinal artery obstruction—1%

- A-AION bilateralisation between 1 and 14 days max. 9 months with bilateral incidence depending on corticotherapy
- A-AION evolution can be:
  - Prolonged for months, with dramatic ophthalmological manifestations, from which cause **A-AION is a diagnosis and treatment emergency, fast and well controlled cortisonic treatment being a must at first signs of ocular and systemic disease** [22]
  - Papillary edema can resorb spontaneously am complete in 6–8 weeks, being followed by total or sectorial optic atrophy depending on the extension of the papillary edema in the acute phase
  - In some cases, VA comeback is NOT obtained
  - Recurrence on initial eye is possible
  - Bilateralisation of A-AION is possible in a few days, which justifies the emergency of initiating the corticosteroid therapy
  - In 50% of A-AION can have an undiagnosed period
- Visual prognosis—reserved through [22]:
  - Progressive aggravation and decrease of sight in weeks, which can be followed by the stabilisation of sight
  - Relapse risk on affected eye
  - Possible bilateralisation

Table 20.4 A-AION differential diagnosis

	A-AION	N-AION
Age	– Frequent 70 years	– Usually 60–70 years
Race	– Caucasian, rarely Afro-American	– No
Sex	– More frequently women	– Man—more frequent
Uni-bilateral	– Unilateral – Bilateral in 2 weeks in 75%	– Unilateral – Bilateral—15%
Simultaneous OA affection	– Occasionally	– Very rare
Secondary affection eye 2	– 75% days, weeks	– Months/years—15–30%
Pre-existent ocular symptoms	– Amaurosis fugaceea – Diplopia	– No
Preceded by systemic symptoms	– Frequent	– No – Risk factors signals present: AHT, SD
General manifestations	– Cephaleea-arthralgia – Myalgia-maxillary claudication	– AHT – SD – Hypercolesterolemy
Pain	– Freuent cephalea, articular pain, maxillary claudication, scalp hyperestesia	– Absent or rare
Optic disc	– Chalky white papillary edema – Choroidal infarction, retinal	– Sectorial papillary edema, hyperemic – Segmentary palor
HSS	>90	<40
GFA	– Choroidal filling defect	– Normal or ON head filling delay
Steroid response	– Systemic – Ocular—sometimes ameliorated sight	– No

A-AION Differential Diagnosis (Table 20.4)

Treatment

- **The disease is an ophthalmological emergency** bilateral blindness being an option
  - Therapeutic methods of methylprednisolone administration [23]
  - Methylprednisolone unique bolus, iv. 250 or 500 mg/day—3 days consecutive
  - Treatment with iv. Methylprednisolone = 3–5 days is continued with oral prednisolone treatment,1 mg/kg/day under periodical clinical and lab control, HSS, PRC at 2–3 weeks

- Oral prednisolone with cortisone dosage decrease after 1–2 weeks, progressive till max 10% initial dose

  80 mg/day = 1–2 weeks
  60 mg/day = 1 week
  5 mg/week decrease till 10 mg/day

- Cortisone treatment duration depends on clinical symptomatology, HSS, PRC
- Corticosteroidian emergency treatment is in adequate dosage, which is the chance of bilateral blindness in A-AION in GCA, but it is useful also for other systemic signs (polyarthralgias) for which chorticotherapy may NOT be immediate and intense [24]

  Emergency installed chorticotherapy is prolonged 2 years under clinical and paraclinical control
  Blindness prevention can be made through guided corticotherapic treatment and adapted to every patient depending on the evolution of the disease, HSS, PRC
  Reactivating GCA is possible especially at the inadequate interruption or uncontrolled decrease of the corticoid doses
  If the disease evolves towards aggravation, it is recommended: **Cyclosporin, Metrotrexate, Tocilizumab**

  Tocilizumab—monoclonal antibody IL-6

  Can be efficient in induction and maintenance treatment of GCA with the possibility of the reduction of the cortisone dose
  Can ameliorate the visual prognosis at patients with severe ophthalmological complications
  Is recommended with:

  Severe ocular lesions
  Bilateral d' embele A-AION
  Aggravation and/or bilateralisation under cortisone
  Limiting secondary effects of corticotherapy

  Antithrombotic treatment
  Anticoagulants—heparin with low molecular weight, preventive dose, at need, curative purpose
  Antiaggregants—aspirin
  Treatment for ameliorating the perfusion in the ON head with vasodilatation: Xantinol, Pentoxifilin

  Their efficiency is not certified

  Papillary treatment edema

  The papillary edema can resorb spontaneously in 8 weeks
  It is recommended to reduce the duration of edema resorbtion to limit the axonal loss

Cortisonic treatment can have positive effect

Neuroprotective treatment

Diphenyl hydantoin
Levodopa
Color with brimonidine
Antioxidants
Capillary protectors
Hyperbaric oxygenation

Secondary prevention for the second eye and/or systemic vascular accidents
Risk factors correction
Visual reduction

Non-arteritic Anterior Optic Neuropathy (N-AION)

- N-AION is an ON infarction generated by the occlusion of the short posterior cilar arteries [25]
- Risk factors
  - Ocular

    Small fiziological excavation
    Cataract surgery

  - General

    AHT
    Diabetes
    Hypercholesterolemia
    Antiphospholypidic syndrome
    Brutal hypotension

- Start at 50–60 years with brutal unilateral drop of VA, with possible affection of the congener eye (20%)
- Symptoms
  - Drop of VA between d.n. and 3/10
  - VF—variable, frequent inferior altitudinal hemianopsia
  - RAPD
- Ophthalmological signs
  - Pale and edematous papilla
  - Linear peripapillary hemorrhages

- Positive diagnosis confirmed by the correlation between the clinical aspect and the lab exam (hemoleukogram, HSS, lypidic balance, glucose), general vascular exam, GRE, GFA.
- Evolution—after 2–3 months, the edema retracts, and the VA can remain stable
  - Nocturnal hypotension can be a risk factor
  - Rare recurrence (2%), with the possible involvement of the second eye (25% in 3 years)
  - Possible optic atrophy after 3–4 weeks.
- Treatment
  - There is no treatment for N-AION, the ischemic process being irreversible
  - The highlight and treatment of the risk factors: hyperlipemy, diabetes, smoking, obesity.
  - Aspirin and vasodilatators to protect the contralateral eye.
  - Ocular hypotension—mannitol, ederene
  - Capillary protectors
  - Antioxidants
  - Hyperbaric oxygen
  - Surgical treatment with ON sheath decompression, optic neurotomy in important VA decrease

Posterior Ischemic Optic Neuropathy (PION) [26]

- PION is generated by retrobulbar ON ischemy.
- PION is frequently bilateral and is followed by important VA drop and VF loss
- Risk factors:
  - Coronary by-pass
  - Lumbar spine interventions
  - Massive bleeding and internal hemorrhage, traumatisms
  - Rarely, after surgery, intraocular injections (more frequently AION)
- Ophthalmoscopic signs;
  - Eyesore initially unmodified or discal edema in the first weeks after acute sight drop.
  - In evolution—optic atrophy
- Reserved visual prognosis

Compressive Optic Neuropathy [27]

- **Anterior form** with papillary edema is given by the ON compression in the orbit, optic canal, intracranial
- ON compression is produced by:
  - Orbitar tumors

    Benignant—glioma, meningioma, hemangioma, dermoid cist
    Malignant—carcinoma, lymfoma, sarcoma, multiple myeloma
  - Orbitar pseudotumors
  - Tiroidian orbitopathy
  - Intracranial lesions (sphenoidal wing meningioma) which can extend to the optic canal with the compression of the intracranial ON, intracanalicular, intraorbitary with papillary edema or papillary palor
- Ocular
  - Progressive VA decrease associated with proptosis and ocular motility limitation
  - VF with "blind spot" enlargement
  - Unilateral papillary edema, horizontal striated folds, verticsl
  - In evolution—optic atrophy
- Signs of orbital pathology with exoftalmy, unpainful, ocular motility disorders, orbitar congestion
- **Posterior form** of the compressive optic neuropathy **is not followed by papillary edema,** but can be followed by neurological signs.
- Compressive RBN is produced by orbitar compression, intracranial through:
  - RB benignant, malignant tumors, pituitary tumor (most frequent), meningioma, craniofaringioma
  - Hidrocephaly
  - Aneurisms
  - Paranasal sinus inflammation
  - Paget disease
  - Tiroidian orbitopathy

Infiltrative Optic Orbitopathy

- Can affect the anterior ON with papillary edema or posterior with RBN and papillary palor.
- Is produced through:

  - Primary tumors: optic glioma, cavernous hemangioma, hemangioblastoma, medulloepithelioma
  - Secondary tumors: metastatic carcinoma, nasofaringioma, lymforeticular tumors (lymfoma, leukemia, multiple myeloma)
  - Infections, inflammations: bacterial, TBC, lues, viruses, fungus, meningitis with cryptococcus in AIDS, sarcoidosis

- Symptoms
  - Progressive decrease of VA depending on the degree of ON affection
  - VF defects: altitudinal, arcuate, hemianoptic, central scotoma, paracentral, centrocentral
  - RAPD

- Clinical signs
  - Anterior or posterior segment inflammation can evolve with progressive or recurring episodes steroid responsive or dependent.
  - Eyesore—if the infiltration affects the proximal segment of the ON, real papillary edema or papillary edema can appear through infiltrative process

- Basis affection treatment
- Corticoid treatment, immunosuppression, radiotherapy
- **Sarcoidosis is the most frequent clinical manifestation in ION** and can be followed by papillary edema or RBN through granulomatous infiltration of the orbitar ON, intracanalicular, intracranial.

Posterior Optic Neuropathy

Retrobulbar Nevritis—RBN

- Retrobulbar optic nevritis—RBN—is the demyelinating infectious inflammatory process, toxic, located at the ON level, after exiting the papilla till the chiasmatic cross, followed by important sight decrease, chromatic feel and visual field, with progressive evolution, spontaneous recovery and relapse, incidence 1–5% more frequent with women 3/1
  - Initially, RBN does not present eyesore modifications in 60% of cases, in 30% exists papillary edema, in evolution, atrophic papilla can be installed

- **RBN is the major cause of sight decrease at young people, it can be the first manifestation in S.M., many patients with RBN do not make S.M.**
- Etiopathogeny of RBN—infectious inflammatory common with the one of the optic nevritis, but an important number of cases with RBN are generated by demyelinating affections—multiple sclerosis.
- **Clinical RBN presents a symptomatological triad with:**

- **Central sight decrease and contrast sensibility with almost integral sight recovery**
- **Periocular pain**
- **Dischromatopsy on the red/green axis with central scotoma and at color** RBN is:
- Acute—acute metilic alcohol intoxication
- Subacute: demyelinating affections of the ON; infectious inflammatory cause, systemic vasculitis
- Chronical: autoimmune affections; alcohol-tabac intoxication

RBN Outside Multiple Sclerosis

Acute RBN in Metilic Alcohol intoxication [28]

- Ocular
- Irreversible bilateral total VA decrease (blind in a few hours) through severe optic neuropathy
- Pale papillary edema, bilateral, with evolution to papillary decoloration with optic atrophy
- Systemic
  - Immediate nausea, vomiting, followed in time by dispnea, cephalea, dizziness, abdominal pain, consciousness alteration, coma, death in respiratory insufficiency
  - Characteristic smell given by the formaldehyde excretion through breath, transpiration
- Treatment
  - Urgent gastric wash, diuretics, purgatives
  - Corticotherapy

Subacute RBN [5]

- Affects more frequent young women between 20 and 40 years old
- Causes
  - Idiopatic
  - Demyelination in MS where RBN evolves with reccurence
  - Bacterial infections, viral, fungal
  - Inflammatory: sarcoidosis, Bechet, Vogt-Koyanagi-Harada
  - Systemic vasculitis: SEL, Sjogren, rheumatoid arthritis, Wegener, GCA, nodous poliartheritis
- Symptoms
  - VA decrease hours, days after the pain debutes

- VA can ameliorate in 6–7 days (weeks) sometimes even without treatment, but dyschromatopsy persists

  VA decrease modified by heat, physical exercise—Uhthoff phenomenon
  Pulfrich phenomenon through which objects that move in straight line can be perceived in a curved trajectory

- Ocular pain, periocular, orbitar (from the inflamated optic nerve sheath), pain which decreases after VA decrease
- Phosphenes, photopsies, photofobia
- VF—central scotoma and at red/green color with peripheric extension of the scotoma
- Red/green axis dyschromatopsia

- Ocular signs [29]

  - Eyesore

    Normal or at 20–35% of patient, optic disc edema
    Rare, peripapillary hemorrhage
    Possible papillary decoloration in time
    Exudative modification of the vitrous in inflammations (sarcoidosis, Behcet)

- Possible bilateral RBN simultaneous or NOT, immediately or later (months).
- Complementary exams for setting the positive diagnosis—MRI, VEP, GRE
- Evolution and prognosis RBN are variable with:

  - Restitution with VA amelioration till normal (65%)
  - Relapse and residual lesions—abnormal contrast sensibility, Uhthoff phenomenon, Pulfrich till optic atrophy (33%)

- Treatment [30, 31]

  - Light unilateral forms—do not need treatment, mandatory clinical surveillance
  - Medium forms, severe—careful treatment
  - **Oral prednisone counter advised because it can affect the second eye and/or can relapse RBN**
  - If the MRI is positive—methylprednisolone 1 g/day × 3 days, followed by oral prednisolone 1 mg/body kg/day on decreasing doses
  - If the MRI is negative, but RBN is bilateral or sight is lost at sequential OA, same treatment as in MRI+

Election medical treatment **in RBN is corticosteroidal treatment** used for:

- VA decrease prevention
- VA stabilisation
- Frequence and severity of the acute RBN reduced
- Congener eye affection limiting [32]

Prime intention treatment

- Treatment with **intravenous METHYL PREDNISOLONE in 250 mg bolus at 6 h/day (SOLUMEDROL 1 g/day)** = 3 or 5 days (severe forms) followed by oral treatment with PREDNISOLONE 11 days—1 mg/b kg/day—low the risk of developing MS in 2 years, but until 5 years there are no modifications comparative with the untreated
- Dexametazone in "plus therapy" = 16–40 mg/day—4 days repeated at 2–4 weeks
  - **Unique oral steroids are not administered because there is a high risk of relapse of the optic neuritis and possible affection of the congener eye.**
  - Corticosteroid treatment has secondary effects: metabolic disorders, gastric ulcer, femural head necrosis, diabetes, pneumopathy.

Corticotherapy recovers VA and diminishes the amelioration interval of sight, but does NOT affect the long term functional result

- Relapse risk of RBN is 28% after 5 years and 35% after 10 years, sometimes the relapse risk is higher.

Relation with MS of the RBN under cortisonic treatment [33, 34]

- I.v. corticotherapy has protective effect in the first 2 years
- MRI determines the risk of MS development at 10 years at 25%

- If visual recovery is not enough
  - I.V. immunoglobulin
  - Plasmtranspherase alters the immunitary response, being used together with corticotherapy

- For RBN in MS it is recommended immunomodulating treatment
  - Beta interferone − 1b = 250 mcq subcutaneous once every 2 days—recommended in progressive MS forms
  - Beta interferone − 1a = 30 meq i.m./week
  - Glatiramer acetate = 20 mg/day subcutaneous
  - = 40 mg × 3/week

- Chemotherapy: azathioprine, methotrexate, cyclophosphamide, endoxan—novantron, natalizumab—monoclonal antibody, ocrelicumab
- Oral agents for MS treatment: fingolimod, teriflunomide, dimethyl fumarate
- Neuroprotective treatment: erithropoetin, simvastatine, fentionine
- **There is no treatment to allow direct remyelination of the ON sheath**
- There is necessary an ethiologic treatment to avoid relapse, disease aggravation and to allow inflammation reduction

RBN in the Presence of MS

Arguments in favour of RBN evolving towards MS

- MRI—demyelinating plaques
- Controverses
  - Retrobulbar ocular pain
  - VF deficit
  - Papillary edema absence
  - Neurological lesions
  - Uhthoff sign
  - Oligoclonal bands in LCR

RBN Diagnosis in MS

- VA drop characteristics—young, woman, VA decrease uni/bilateral (rare)
- Feeling of stopping
- VA drops relatively fast (hours → weeks)
- Can evolve to blindness
- In 70% associated with pain at eye movement

MS Suspicion

- Visual disorders antecedents
- RAPD—evocative for anterior unilateral touch of the ON
- Eyesore
  - Normal aspect at first episode
  - Palor >5%
  - Rare anterior segment inflammation or cornean anesthesy
- Oculomotor affection signs
  - Anterior internuclear affection—adduction palsy at one eye, contralateral abduction nystagmus
  - CN VI, III, IV affection
  - Nystagmus tied or NOT to the anterior internuclear affection
- Ocular recurrence
- RBN episodes associated with neurological signs: dizziness, parestesis, Uhthoff sign (aggravation of the symptoms then the body temperature rises in physical effort, summer season, warm baths)**Complementary exams which confirm RBN unilateral and can decel infraclinical contralateral affection**

- Central VF with paracentral scotoma
- Farnsworth test desaturated 15 Hue—Dyscromatopsy red/green
- VEP–P100 wave abnormalities, elongation, amplitude diminishing, bilobed aspect

- **Patients with recurring RBN episodes can develop MS chronical RBN—** alcohol-tabac intoxication

- RBN at smoking and drinking patients, with protein diet deficits, B complex
- Frequent man between 40 and 60 years old, exposed to alcohol-tabac intoxication.
- Ocular
  - Initially VA can be normal, but with minimal modifications of the contrast sensibility and accommodation disorders.
  - In time RBN with:

    Progressive bilateral VA decrease
    VF—nasal scotoma, pericaecal. Centrocaecal
    Red/green axis dyscromatopsy
    Eyesore in time, peripapillary decoloration

- Treatment
  - Eliminating the toxic (smoking, alcohol)
  - Multivitamins (group B)
  - Antioxidants
  - Vasodialtators
  - Nutrition amelioration

Devic Optic Neuromyelitis (DNM)

DNM is characterised through ON affection and spinal cord simultaneous or decaled, with monophasic recurring evolution in 2/3 of cases of optic neuritis and transverse myelitis episodes with longitudinal extension of the spinal cord lesions at MRI (more than 3 segments) [35]

- Frequent bilateral affection
- Acute severe VA decrease (till blindness)
- Normal cerebral MRI
- Palsy, respiratory insufficiency, death
- Treatment with:
  - High intravenous doses of cortisone continued with oral treatment
  - Immunosuppression: rituximab, microphenolate mophetyl, azathioprine

Devic disease can be associated with:

- Systemic eritematous lupus
- Conjunctive tissue diseases—Sjogren syndrome
- Pulmonary tuberculosis

Optic Neuropathy and Multiple Sclerosis at Children

The disease has different clinical aspects at children

- Children or teenagers with demyelinating optic neuritis can develop later MS
- Children with optic neuritis have a similar disease with the adults, but higher percent 50/75% of children have **bilateral sight decrease and papillary eyesore edema**
- Treatment = methylprednisolone i.v. 4 or 15 mg/kg/day initially followed by oral prednisolone 1 mg/kg with doses reduction
- **Generally good prognosis for children, 80% recover VA**
- Etiological, optic nevritis at children is:
  - Immune mediation, post infectious (post viral, varicella)
  - Febrile states after vaccination
  - Meninges, orbit, sinus inflammation
  - Infections—pox, Lyme, mononucleosis
  - Idiopathic—possible genetic predisposition with late demyelination
  - Isolated forms of optic neuropathy with normal MRI (does NOT develop MS)
  - Recurring forms can develop MS (10–50%) after 7 years (median) with MRI abnormalities
  - Optic neuritis at children is frequently the first clinical manifestation of MS

Infectious Inflammatory Optic Neuropathy: Clinical Forms

Inflammatory Optic Neuropathy Associated with Bacterial, Viral, Parasitar Infections

- BACTERIAL infections
  - Ocular tuberculosis
  - Ocular primary or secondary pox with papillitis end neuroretinitis
  - Lyme disease
  - Whipple disease
  - Cat claw disease—benignant lymforeticulosis associated with neuroretinitis
- Viral infections—HSV, HZV, CMV, HIV
  - Acute retinal necrosis—ARN
  - Progressive retinal necrosis—PORN
  - CMV retinitis
  - Oftalmic zone
  - Cryptococcus meningitis in AIDS with acute optic neuropathy
- Parasitar infections

  - Toxoplasma
  - Toxocara
  - Oncocercoza
- Micosis
  - Candida albicans, Aspergillus cryptococcus, histoplasma

Infectious Optic Neuropathy in Demyelinating Affections

- Multiple sclerosis
- Devic neuroretinitis
- Acute disseminated encephalomyelitis
- Idiopathic optic monophasic neuropathy or with relapse

Infectious Optic Neuropathy in Systemic Inflammatory Diseases

- Sarcoidosis
- Systemic erhitematous lupus
- Nodous polyarteritis
- Wegener granulomatosis

Immune Mediated Inflammatory Optic Neuropathy

- Bechet disease
- Vogt-Koyanagi Harada Syndrome

Optic Neuropathy Associated with Neurological Manifestations

- Susac syndrome
- Acute multifunctional posterior multifunctional placoid
- Eales disease

Inflammatory Optic Neuropathy Associated with Bacterial Infections [29, 36]

- Ocular tuberculosis
- Primary and secondary ocular pox

Whipple Disease

- Inflammatory disease of the large intestine, which is followed by malabsorption.
- Systemic
  - CNS affection
  - Cutaneous hyperpigmentation
  - Cardiopulmonary determinations
  - Arthropathy
- Ocular
  - Intermediar, anterior, chronic, rare uveitis
  - Optic neuropathy

Cat Claws Disease

- Selflimited disease produced by Bartonela henselae through the scratch of an infected cat.
- It is manifested through oculoglandular syndrome 5–10%
  - Chronic fever
  - Regional adenopathy
  - Follicular conjunctivitis
  - Posterior pole manifestations

    optic neuropathy 1–2%
    neuroretinitis with optic disc edema (exudates)
    vitritis
    focal retinochoroiditis and intraretinal white spots
    macular star
    retinal venous and arterial occlusions (rare)
- Visual prognosis—good
- Systemic

  - Variating clinical manifestations from benignant selflimited forms to severe forms with endocarditis and hepatitis

- Treatment
  - Antibiotic: rifampicin, gentamicin, ciprofloxacin, sulfmetoxazole-trimetropine

Lyme Disease

Systemic disease produced by the infection with Borelia burgdorferi transmitted through the sting of capua, Isodex damini, neurological manifestations, ophthalmological, articular dermatological, with stadial evolution.

Ocular
- Neuroretinitis
- Optic neuropathy
- Retinalvasculitis
- Intermediary uveitis
- Conjunctivitis
- Interstitial keratitis
- Neuroophthalmological lesions: cranial nerve palsy

Treatment
- Antibiotics:
- Tetracycline, doxycycline, erithromicine or peniciline, if tetracycline is NOT recommended, ceftriaxone

Inflammatory Neuropathy in Viral Diseases [37]

Viral Infections: HSV, HZV, CMV, HIV

Cytomegalovirus Retinitis (CMV)

- It is present at patients with AIDS and characterised through culminant retinitis with white granular infiltrates, slowly progressive, extended along the retinal vessels with peripheral debut.
- Complicated with optic atrophy and RD
- Treatment
  - Ganciclovir

    Systemic = 5 mg/kg i.v. × 3/day for 2–3 weeks, than 90–120 mg/day—secondary effects: nephrotoxicity, neutropenia, uveitis
    Intravitrean—Fomivirsen

Prognosis—reserved, 50% decrease in 6 months.

Acute Retinal Necrosis—ARN

- Devastating retinitis characterised through
  - Retinal vasculitis
  - Hemorrhages
  - Retinal peeling off
  - Retinal necrosis
  - Vitrean inflammation
  - Optic nevritis
- Primary produced through HSV infection, Zoseter varicella (VZV), cytomegalovirus (CMV) and Epstein Barr
- Needs immediate treatment with:
  - Oral antiviral agents and intravitrean—acyclovir
  - Steroids for reducing the inflammation
  - Surgical treatment and laser for retinal complications

External Progressive Retinal Necrosis: PORN

- The infection produced by the varicella Zoster (HZV) present at patients with AIDS—characterised through rapid progressive sight decrease uni, bilateral

Ocular
- Retinal multifocal white/yellow infiltration
- Focal halitis
- Optic neuropathy
- Retinal necrosis with precocious macular touch

Treatment
- Ganciclovir i.v. alone
- Foscarnet in association

Prognosis—reserved.

Inflammatory Optic Neuropathy in Parasitary Infections

- Toxoplasma
- Toxocara
- Oncocercosis

Inflammatory Optic Neuropathy in Micosis

– Candida albicans, cryptococcus, Aspergillus, histoplasma

Inflammatory Uninfectious Optic Neuropathy in Systemic Diseases

Optic Neuropathy in Sarcoidosis

- Sarcoidosis is an idiopathic systemic disease with unknown ethiology, characterised through granuloms with epithelioid noncaseous cells more frequent with women, which affects predominant the lung
  - Isolated visual signs debut, neurological signs or variable symptoms with: fever, diarrhea, pulmonary symptoms, lymphadenopathy (hilar)
  - Affects

    lung 90%
    CNS—5% with:

  - CN palsy
  - Aseptic meningitis
  - Peripheral neuropathy
  - Ocular touch

    Anterior segment

  - Interstitial keratitis
  - Anterior uveitis

    Acute—young adult with brutal debut sarcoidosis
    Chronical—granulomatous which affects old people with chronic pulmonary sarcoidosis

  - Trabecular nodules
  - Lacrimal gland with keratoconjunctivitis sica
  - Conjunctiva—follicles, granuloms, conjunctival flictens
  - Sclera—scleral nodules
  - Intermediary uveitis
  - Orbitar inflammatory syndrome
  - Posterior segment (retinal)
  - Vasculitis with retinal periflebitis

    Focal
    Perivenous exudates
    Retinal venous branches occlusions

- Chorioretinitis, choroidal nodules
- Vitrean infiltrates
- Granuloms: choroidal, retinal, papillar, preretinal—Landers sign
- Peripheral retinal neurovascularisation
- Optic nerve
- Papillary edema
- Optic neuropathy
- Optic perinevritis

Treatment

- Steroids, sometimes with treatment resistance, with fibrosis development of the ON sheath
- Rituximab or mofetil microphenolate

Systemic Eritematous Lupus

- Multisystemic associated disease with ANA which affects: skin, articulations, kidney, NS and eyes,
- **Half of the cases with SEL have optic neuropathy associated with transverse myelitis** (miming Devic disease)
- ON dysfunction presents different forms:
  - **Primary retinal vasculopathy** (3–30%)
  - Retinal flebitis
  - Vitrous hemorrhage
  - Retrobulbar optic neuritis
  - Papillitis
  - A/P-ION
  - Papillary edema associated with cotonous exudates, hemorrhages, neovascularisation
  - Different degree vascular occlusions on the small vessels
- Neurological complications in 20%:
  - Encephalopathy
  - Vasculitis
  - Myelitis
- Treatment
  - I.v. corticoids Methylprednisolone 3 days, followed by oral corticoids 1 mg/kg/day

    Immunosuppressives alternating with cytotoxics: chlorambucil, metrotrexate, azathioprine, infliximab, cyclosporin, mofetil microfenolate, cyclophosphamide

Wegener Granulomatosis

- Idiopathic necrotizing vasculitis of the small vessels with granulomatous inflammation characterised through granuloma located in the superior and inferior airways (lungs), NS, kidneys.
- Systemic
  - To 50 years
  - Pneumonia
  - Sinusitis
  - Renal affection
  - Neurological—one in four patients with:

    Peripheral neuropathies
    Ophthalmoplegia
    Stroke
    Epilepsy
    Encephalitis
- Ocular manifestations are present in 50% of cases:
  - Orbit involvement and orbital extension with erosions and osseous dysfunctions
  - Scleritis, episcleritis
  - Uveitis
  - Marginal cornean ulcer
  - Conjunctival involvement and neuro retinal with variated clinical manifestations from unpainful inflammations till major explosive inflammations

    Optic neuropathy with papillary edema
    Retinal vasculitis

Treatment
- Chorticosteroids
– Immunosuppressives: methotrexate, cyclophosphamide, rituximab

Nodous Polyarteritis

- Nodous polyarteritis is a vasculitis which affects medium and small calibre arteries, with segmentary inflammation and fibrinoid necrosis
- Systemic—affects the kidney, heart, liver and g.i. tract after 40 years
- Ocular
  - Choroidal and retinal ischemia produced by unspecific vasculitis
  - Optic neuropathy
  - Unspecific orbitar inflammation (rare)

Immune Mediated Inflammatory Neuropathies

Bechet Disease

- Bechet disease is a multisystemic idiopathic vasculitis associated with HLA-51
- It is characterised through the clinical triad:
  - Oral and genital ulcerations with relapse
  - Iritis with hypopyon, panuveitis with severe evolution
  - Cutaneous lesions, nodous erythema
- Ocular manifestations are present in 70% of cases
  - Anterior acute uveitis with hypopyon
  - Panuveitis
  - Scleritis
  - Retinalvasculitis with retinitis, periflebitis and periarteritis
  - Retinal venous occlusion
  - Cystoid macular edema
  - Subacute unilateral optic neuropathy with VF defects, papillary edema and retinal vasculitis
  - Optic atrophy
- Systemic manifestations
  - Skin

    Nodous erythema
    Pustulous eruptions
    Pseudofoliculitis
  - Articular affection: knee, hip
  - Pulmonary affection, g.i. tract, kidney
  - Thrombosis and systemic vasculitis, associated arterial aneurisms
  - Neurological 5–10% with inflammation in: brain, spinal cord, nervous roots, cavernous sinus thrombosis

    Many forms of Bechet disease debut with neurological manifestations

Treatment

- Chorticosteroids
- In occlusive vasculitis—azathioprine, cyclophosphamide
- Immunosuppressives

  Azathioprine, tacrolimus, chlorambucil, cyclophosphamide
  Levamisole, colchicine, dapsone
  Biological therapy: infliximab, monoclonal antibodies, anti TNF alpha
  Adalimumab, etanercept

Vogt-Koyanagi-Harada Syndrome—VKH

- VKH syndrome is an uveomeningeal syndrome which includes: the eye, skin, meninges and ear and which affects pigmented individuals
  - Common target can be tied with the presence of melanic cells in these organs
- **Frequent disease in Japan (after Bechet) is characterised through granulomatous bilateral uveitis associated with various cutaneous manifestations, auditive and NS affection symptoms**
  - T-cells immune mediated response can be involved against melanocytic antigens
  - There have been reported severe cases of VKH in association with interferon alpha-2b-RIBAVIRINE in hepatitis treatment and MS
- Systemic
  - Neurological

    Cephaleea
    Aseptic meningitis (meningism)
    Neurosensorial hearing decrease
    Tinnitus, dizziness
    Encephalopathy
    Pleiocitosis-lumbar punction with limfocites and monocites
  - Cutaneous

    Alopecia
    Poliosis (hair depigmentation)
    Vitiligo (skin depigmentation)
- Ocular
  - Bilateral anterior granulomatous chronic uveitis with irian synechiae and complicated cataract
  - Posterior uveitis
  - Open or closed angle granuloma glaucoma—40%
  - Retinal peel off, inferior exudative at debut, with spontaneous reapplication
  - Pigmentary modifications in EPR
  - Multifocal choroid
  - EMC
  - Acute progressive optic neuropathy, chronic with papillary edema and papillary and retinal neovascularisation
  - Vitrean hemorrhages

Treatment

- Corticosteroids in large doses for a few months with progressive decrease of doses

- Incomplete answer at corticosteroids is possible
- RD responds at cortisonic treatment
– Immunomodulators: mofetil microphenolate, cyclosporine, azatioprin
– Intravenous immunoglobulin
– Biological agents: infliximab, adalimumab

Optic Neuropathy Associated with Neurological Manifestations

Susac Syndrome

- A brain, retina and inner ear microangiopathy, rare affection, immune mediated, present at young women—30 years
- Clinical
  – CNS symptom debut (2/3 of patients), followed by retinal arterial obstruction in 90%, and in 60% bilateral and then by hearing modifications
  – Clinical triad

    Encephalopathy
    Retinal arterial vascular obstruction
    Hearing sensorio-neural decrease

  – Difuse vasculo-occlusive modifications at the ON head and the peripheral retina
  – Present encephalopathy in 44% of patients with difuse microinfarctions, multiple cerebral

    Cortical MRI modifications and in callous body with thinning and vascular sclerosis
    Some patients can have severe neuro-psychical deficits

- Treatment
  – Early aggressive
  – Steroids
  – Immunosuppressives: mofetil microphenolate, rituximab

Placoid Pigmentary Multifocal Posterior Acute Epiteliopathy—APMPPE

- Is a self-limited chorioretinitis, bilateral acute which affects the young adult, tied (possibly) with an anterior virosis

- Visual symptoms
  - Foggy sight
  - Photopsies
  - Scotoma
- Ophthalmoscopic
  - White/gray multifocal lesions located uni/bilateral at the EPR level in the optic disc area and in the posterior pole
  - Abnormal EPR results from the choroidal vascular dysfunction induced by the obstructive vasculitis
  - Edema located at the ON head
  - Chorioretinal vasculitis
- Neurological signs
  - Cephalalgia
  - Transitory ischemic attack
  - Hearing deficit
  - Tinnitus
  - Cerebral vasculitis
  - Stroke—in 60%
- Treatment
  - Corticoids most frequently associated with
  - Immunosuppressives—cyclophosphamide for 6–12 months
- Visual prognosis
  - Good if the macula is not involved
  - Decreased at older people

Optic Perinevritis

- Chronic inflammation, unspecific of the ON sheath, sometimes granulomatous, associated with different degrees of fibroplasty and collagen deposits
  - Bilateral optic neuropathy with relative maintaining of central sight
  - Ocular pain
  - MRI modifications with ON sheath affection
  - Responsive at corticoids in high doses
- Optic inflammatory perinevritis ethiology:
  - Acute orbital inflammation (orbital pseudotumor) with: proptosis, palpebral edema, muscular affection and posterior scleritis
  - Systemic cause perinevritis: sarcoidosis, pox, Lyme, HSV, TBC

  - Idiopathic

- **Distinction between optic nevritis and perinevritis bases on the radiological differentiation of the ON sheath**
- Clinical, optic perinevritis presents:
  - Old people
  - Frequent bilateral affection
  - Optic disc affection with venous retinal secondary stasis, vascular dilatation, retinal hemorrhages, peripheral
  - VA with relatively good function
  - Can develop progressive insidious optic neuropathy

Toxic, Metabolic, Nutritional Optic Neuropathy [38, 39]

- Endogenous toxics—diabetes, anemia, pregnancy, burns
- Exogenous non-medicamentous toxics—arsenic, lead
- Exogenous medicamentous toxics—amiodarone, chlorambucil, etambutol, methanol, rifampicine, quinine, tamoxifen
- **Acute toxic neuropathy in methilic alcohol intoxication**
- **Chronic toxic neuropathy in alcohol-tabac intoxication**
- **Amiodarone intoxication neuropathy**
  - Amiodarone is used in treating cardiac arithmias, it can accumulate inside the tissues (cornea, retinal ganglionar cells)and give toxic neuropathy
  - Ocular

    VA progressive decrease uni/bilateral
    Cornea verticillate
    Non-arteritic ischemic anterior optic neuropathy with discrete bilateral papillary edema.

  - Variable prognosis
- **Etambutol intoxication neuropathy**
  - Ocular

    Systemic bilateral VA decrease
    Symmetric dischromatopsy, bilateral red/green
    Central scotoma
    Eyesore—normal papilla or slightly prominent with hemorrhages in flame, in time—optic atrophy

  - Treatment stop or discontinuous treatment

Nutritional Optic Neuropathy

- Can be present in deficitary diet (vegetarians, alcoholics), B12, B1, B6, B2 vitamins, folic acid deficit, Biermer anemia
- Ocular
  - Slow VA decrease, bilateral, symmetrical, sometimes serious
  - Central scotoma
  - General dischromatopsy
  - Eyesore

    Hyperemic optic disc with peridiscal hemorrhage or without eyesore modifications
    Evolving optic atrophy
- Affection present at any age, with risk factors: drug addicts, smokers, alcohol use, deficitary diets.

Hereditary Optic Neuropathy

- Symmetric, bilateral, followed by central VA decrease and central scotoma, caeco-central and are genetically determined.

LEBER Hereditary Optic Neuropathy

- Man, debut 15–30 years
- Ocular
  - Unilateral VA decrease (1/10) followed by the affection of the other eye in days, months and progressive VA degradation
  - VF abnormalities with caeco-central scotoma
  - +- RAPF
  - Severe dischromatopsy
  - Eyesore—dilatated papillary capillaries, vascular tortuations, peripapillary nervous fibers bulging (pseudoedema)
- Reserved prognosis
- LEBER syndrome—optic neuropathy, spasticity, encephalopathy, myelopathy.

Kjer Optic Atrophy

- DA, OA bilateral, symmetrical with debut at 4–8 years
- Ocular
  - VA is reduced insidious, progressive, systemic
  - VF-central scotoma
  - Yellow/blue dischromatopsy
  - Nystagmus
  - Eyesore—temporal or difuse optic atrophy
- Systemic—rare hypoacusion

Behr Optic Atrophy

- RA, debut in the first decade of life with heredo-familial optic atrophy associated with ataxia
- Ocular—difuse optic atrophy with variable prognosis
- Systemic—ataxia, mental retar, pyramidal tract signs, corea, spastic paraparesis

Wolfram Syndrome

- RA, debut 10–20 years.
- Ocular—difuse optic atrophy with reserved prognosis.
- Systemic—anosmia, ataxia, epilepsy, mental retard, small size, insipidous diabetes, CRF protein growth.

Optic Atrophy [40]

- An irreversible degenerescence of the pregeniculate fascicles of the ON (ganglionar cell cilindraxes) in which ophthalmoscopic, the papilla is white-pale gray associated with VA decrease, VF modifications and chromatic sense.
- Temporal decoloured papilla is not pathological (can be familiar)
- Optic atrophy is the consequence of a pathological process which affects the ON in diverse retinal, orbital, chiasmatic, optic tract, LGC diseases and can be:
  - Ascendent atrophy in retinal ganglionar cells lesions in: granulomatous atrophy, RCAO, chorioretinitis, post papillary edema.
  - Descendent atrophy in primary atrophy (PGP, tabes), RBN in MS, posttraumatic, tumors, meningitis, decrepitude.

- Mixt—toxic nevritis, diabetes.

- Symptoms
  - VA decrease
  - Variable VF amputations (central scotoma, central amputations, peripheral, hemianoptic deficit)
  - Light sense modifications

- Ocular—ophthalmoscopic
  - Difuse white/pale/grey papilla or located with concave meniscus till the cribrosa lamina, with nete margins
  - Narrow arteries or completely obstruated

- Optic atrophy can be:
  - Partial OA

    More frequently temporal OA
    In horizontal plane with horizontal hemianopsia in tumors; optochiasmatic arahnoiditis (through compression)

  - Total OA

    Vascular lesions
    Papillary postedema
    Glaucomatous excavation
    Chorioretinal diseases
    RD

- Optic cup modifications
  - Glaucomatous excavation with profound atrophy with visible cribar lamina with vessels which turn at the edge of the excavation.
  - Non-glaucomatous excavation in: inflammations, compression, trauma.

After etiology OA is:
PRIMARY OA (clinically identified, frequently, late)

- Very low VA (cecity)
- Ophthalmoscopic

  White/porcelanous, grey papilla
  Nete papillary contour
  Visible perforated lamina (willow center)
  In time, vascular narrowings

- **Tabetic optic atrophy, PGP**
  - Appears at 15–20 years after luetic infection, bilateral
  - Ocular

Cecity
Grey papilla
III, IV, VI palsy
Argyll Robertson sign with miosis, pupilar inequity

- **Hereditary optic atrophy**
  - Isolated—Leber OA
  - Followed by neurological syndromes: Hurler, Bardet-Biedl, Friedrich disease, Pierre-Marie, syringomyelia, spastic paraplegy.**SECONDARY OA**

– White/pale, white/grey, white/yellow papilla with erased, irregular margins, with pigmentary margin
– Lamina criblata not visible
– Post-inflammatory—narrowed arteries, dilated veins
– Post-stasis—slight papillary prominence

- Secondary OA causes
  - **Inflammatory processes in:** retinal inflammation, ON (papillitis, RBN), meningitis, optochiasmatic arahnoiditis
  - **Degenerative processes in:** VLMD, Stargardt, Tay-Sachs, myopia, angioid striations, PR, diabetes, gout, neurological diseases (MS, lateral amiotrophic sclerosis), RCAO, RCVO
  - **ON compressions in:** ICHT, inflammations, traumatisms, orbitar tumors, intracranial tumors.
- Secondary OA prognosis is dependent on the cause.
- Treatment—inexistent in total OA.

Ocular Affection in the Pathology of the Chiasma

- Chiasmatic pathology with ocular affection is given by:
  - Tumors

    Pituitary adenoma
    Craniopharyngioma
    Meningioma
    Glioma
    Metastasis

  - Non-neoplasic affections

    Aneurisms
    Rathke pouch cist
    Fibrous displasy
    Sphenoidal sinus mucocele

Arahnoidian cists

– Other diseases

Demineralisations
Inflammations
Traumatisms
Vasculitis

Pituitary Adenoma

- Anterior pituitary tumor which secrets or not hormones
  - Disease with debut at 30–50 years with cephalalgia, visual and endocrine disorders
  - Ocular

    VF alteration with bitemporal hemianopsy with superior debut
    Colour desaturation (early sign of chiasmatic touch)
    Optic atrophy (50%)
    Diplopia secondary to a lateral extension in the cavernous sinus

  - Endocrine modifications
  - Nystagmus
  - CT shows erosion or saddle enlargement
  - MRI—hiposignal in T1, hiposignal in T2
  - Treatment

    Surgical in severe compressions, if the medical or radio treatment fails
    Radiotherapy
    Stereotaxic radiotherapy for cavernous sinus invading adenoma
    Medical with dopaminergic (carbogoline) bromocriptine in prolactinoma

- Other causes of bitemporal hemianopsy: dermatoslazis of the superior eyelid, ON coloboma, nasal retinoschisis

Craniopharyngioma

- Slow growth tumor, originating in the remains of the Rathke pouch along the pituitary beam.
- At child—growth disorders, sexual development disorders, obesity
- At adult—VA decrease, VF modifications with bitemporal hemianopsy with inferior debut.
- CT—calcifications, MRI—isosignal in T1, hypersignal in the cystic component

- Treatment—surgical with post-surgery radiotherapy, but with frequent relapse

Meningioma

- **Clinical forms**
  - Saddle meningioma—compresses the chiasmatic cross of the ON and generates homolateral central scotoma
  - Sphenoidal meningioma—early ON compression if the tumor is median, late if the tumor is on the lateral edge of the sphenoid and of the median cranial fossa.
  - Olfactory meningioma—anosmia and ON compression.
- Treatment—surgical, radiotherapy.

Optic Affection in Optic Bandelet Pathology

- The optic bandelet starts in the chiasma through the cerebral peduncles till the LGB; in every bandelet there are direct and crossed fibres.
- Clinical
  - Noncongruent homonym hemianopsy
  - Wernicke hemianoptic pupil

    MFR—normal when the integer hemiretina is stimulated
    MFR—absent when the damaged hemiretina is stimulated
- Optic atrophy
- Contralateral pyramidal signs

Occular Affection in Lesions of the Optic Radiation

- Temporal radiations
  - Ocular

    VF alteration with homonym superior contralateral quadranopsy
    Visual hallucination
  - Systemic

    Olfactory and gustatory paroxistic hallucination
    Epilepsy

Disphasy

- Anterior parietal radiations
  - Ocular

    VF altering with homonym superior contralateral quadranopsy
    Visual perception difficulties

  - Systemic

    Agnosia
    Right/left confusion
    Acalculia

- Main radiations
  - Ocular—complete homonym hemianopsy

Ocular Affection in Striated Cortex Lesions

- VF alterations
  - Posterior cerebral artery occlusion (PCA) produces congruent homonym hemianopsy
  - Occipital cortex lesions can produce macular congruent homonym deficit
- Cortical cecity is associated with:
  - Visual halucinations—Anton syndrome (Denys cecity)
  - Mobile visual target perception, Not the static one (Ridoch phenomenon).
- Causes
  - Vascular lesions in PCA (responsible for 90% of isolated homonym hemianopsys)
  - Migrene
  - Traumatisms
  - Tumors

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Chapter 21
Ocular Tumors

Marieta Dumitrache

Abstract **Eyelid tumors** are: benign tumors, congenital, acquired, malignant tumors (baso cellular, spino cellular, carcinoma sebaceous, malignant melanoma). **Conjunctival tumors** are benign, malignant tumors, degenerative disease (Pinguecula Pterrygion). Orbital tumors are benign, malignant (optic nerve glioma, meningioma, neurofibroma, limfosarcoma, sarcoma Ewing). **Tumors of the iris, cilliary body**, benign, malignant. Choroid tumors benign, and malignant tumors, **choroidal melanoma 85%** of uveal melanoma is the primary intraocular tumor, the must common in adult with variable evolution (extension in the orbit, blood metastasis in the liver, lung, CNS). Treatment: brachytherapy, external radiotherapy, enucleation, exenteration, chemotherapy. **Tumors of the retina and optic nerve:** congenital tumors (hemangioma), phacomatosis. Retinal malignant tumors are **retinoblastoma**, primitive intraocular malignant tumor most common in children detected by leukocoria, strabismus, exophtalmie, secondary glaucoma, uveitis, and laid to distant metastasis with intracranial hypertension. Treatment: long section, enucleations of optic nerve (more than 5 mm), external radiotherapy, brachie, cryotherapy, chemotherapy in metastatic tumors.

Keywords Eyelid · Conjunctival · Orbital · Iris · Cilliary body · Tumor benign, and malignant · Melanoma choroidal · Retinoblastoma · Enucleation Radiotherapy · Chemotherapy

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Eyelid Tumors: Tables 21.1, 21.2, 21.3 and 21.4

Table 21.1 Congenital benign tumors

Flat capillary hemangioma	• Two forms – Slightly prominent red spots, frequently located on the upper eyelid (regression after 5–6 years) – Nevus flammeus—angiomas in territory V—Sturge-Weber syndrome	– Intralesional steroids – Laser coagulation – Surgical resection
Tuberous (cavernous) hemangioma	– Reddish, bluish lobulated protrusions in the area of the commissures, with possible regression after 5–6 years	– Intralesional steroids – Laser coagulation – Surgical resection
Dermoid cyst	– Dysembryonic tumor that may contain hair follicles, sebaceous glands, sweat glands, sebum, located in the internal or external angle	– Surgical resection – Recurrence if extirpation is incomplete

Table 21.2 Acquired benign tumors

Papilloma	– It can be sessile or pedunculated	
Flat warts	– They occur in adults and are slow growing	
Seborrheic keratosis	– Brown lesions on a verrucous surface	
Pyogenic granuloma	– Bleeding pink mass with rapid increase after trauma	– Excision with cauterization of the base
Keratoacanthoma	– Rarely, rapidly growing nodules with a keratin-filled crater that spontaneously involutes after several months – Requires differential diagnosis, with basal- and squamous cell carcinoma	
Melanic tumors (melanocytic nevus)	– Are palpebral lesions with variable papillomatous or flat pigmentation – By location they are: intradermal, junctional (between dermis–epidermis) with malignant and mixed potential – Low risk of malignant transformation (high for superficial ones)	– Surveillance and, if necessary, surgical excision
Xanthelasma	– Yellowish, oval, slightly prominent tumors, located in the inner portion of the eyelid and periorbitally	
Tumors of the hair follicle	– Trichoepithelioma, trichofolliculoma	

Table 21.3 Precancerous lesions

Actinic keratosis	– Flat, hyperkeratotic lesion located on the face, eyelids, scalp, which may progress to basal cell carcinoma	• Biopsy followed by: – Excision Cryotherapy
Dubreuilh's melanosis	– Pigmented macules with slow evolution towards melanoma – Clinical surveillance for the risk of malignant transformation	

Table 21.4 Malignant tumors

Basal cell carcinoma BASOCELLULAR	– 80% of malignant eyelid tumors – Nodular, firm, pearly tumor with dilated vessels on the surface or ulcerated nodular tumor at the margin of the lower eyelid (toward the inner angle) or poorly demarcated sclerosing tumor at the margin of the eyelid – Local malignancy; it rarely metastasizes	– Biopsy and excision within oncological limit with skin graft – Radiotherapy – Cryotherapy – Carbon dioxide laser
Squamous cell carcinoma SPINOCELLULAR	– Rare tumor 2–5%, aggressive with high capacity to extend deep into the orbit, adjacent sinuses (maxillary, ethmoidal)	– Biopsy and surgical treatment within oncological limits – Radiotherapy – Chemotherapy if needed
	– Varied clinical appearance: erythematous hyperkeratotic plaques or ulcerated tumors with congested base with hardened and everted margins with possible dissemination	
Sebaceous carcinoma	– Aggressive, rare tumor that develops from the meibomian gland, present in older women, confused with chronic blepharitis or recurrent chalazion – Nodular, infiltrated appearance with marginal palpebral thickening and localized madarosis or extensive pagetoid infiltration in the conjunctiva – Very rarely nodular or ulcerative Zeiss gland carcinoma at the eyelid margin with slow growth	– Tumor excision with cryocoagulation after biopsy – Radiotherapy
Malignant melanoma	– Flat lesion with irregular borders and variable pigmentation or hyperpigmented (black) nodular lesion with possible nodal invasion and metastasis	– Wide excision within oncological limit in surface and depth – Radiotherapy Chemotherapy as a palliative method in advanced cases

(continued)

Table 21.4 (continued)

Sarcoma	– Exceptional	
Kaposi's sarcoma	– Red, violaceous vascular nodule that occurs in AIDS	– Palliative radiotherapy if needed
Malignant lymphoma	– Rarely at eyelids	
Burkitt lymphoma	– Present in African children – Possible association with Epstein-Barr virus	
Neurofibroma	– Associated with neurofibromatosis	
Schwannoma (also called neurilemoma)	– Located in the inner angle	
Merkel cell carcinoma	– Rare tumors, located in the upper eyelid, with rapidly evolving violet nodules and intact skin	

Conjunctival Tumors: Tables 21.5, 21.6, 21.7, 21.8, 21.9, and 21.10

Table 21.5 Benign non-pigmented tumors

Epibulbar dermoid cyst	– The most common congenital tumor in children, located infero-temporally on the smooth, yellowish-white tongue (contains hair follicles, sebaceous glands), small round + vascularized tumor – At ocular level, it can be associated with: palpebral coloboma, ocular coloboma, aniridia, microphthalmia – Systemically, it can be associated with: Goldenhar syndrome, Treacher Collins, Franceschetti syndrome	– Excision in small lesions – Corneal lamellar or scleral graft for voluminous lesions
Epibulbar lipodermoid	– Mobile subconjunctival mass, located in the external canthus in adults, that can be complicated with: ptosis, corneal dryness, motility disorders	– Excision in complications
Pyogenic granuloma	– Vascularized, budded conjunctival formation that develops after trauma to the conjunctiva	– Excision with cauterization of the base
Papilloma	– Pediculated—in papillomavirus type 6–11 infections with single, multiple papillomatous lesions located on the palpebral conjunctiva, fornix, caruncle	– Spontaneous healing – Biopsy and excision with cryotherapy for large tumors – Subconjunctival injections with interferon, mitomycin in recurrent forms
	– Sessile—isolated, juxtalimbic on the bulbar conjunctiva	– Excision
Granuloma		
Adenoma		
Fibroma		
Angioma		
Keratoacanthoma		

Table 21.6 Benign pigmented tumors

Nevus	– Conjunctival tumor with malignant potential with diverse pigmentation and vascularization, located on the bulbar conjunctiva, juxtalimbic, semilunar fold, flat or slightly raised, well demarcated – Signs of malignant potential: corneal extension, increase in volume or pigmentation, vascularization	– Excision when it becomes unesthetic or potentially malignant

Table 21.7 Melanosis and melanocytosis

Epithelial melanosis (racial)	– Areas of brown pigmentation, flat, predominantly on the limbus, bilateral in melanodermic individuals	
Primary acquired melanosis (PAM)	• Has two forms: – PAM without atypia is a benign proliferation of normal melanocytes	– No need for treatment
	– PAM with atypia, with precancerous lesions, with a risk of malignant transformation in 5 years, with areas of brown pigmentation, irregular, uni-multifocal	– Excision of small lesions – Cryotherapy or mitomycin in large lesions
Congenital melanocytosis	• Has three forms: – Ocular—subconjunctival multifocal gray pigmentation – Cutaneous—affects only facial skin with hyperpigmentation – Oculocutaneous—nevus of Ota—with eyes, facial skin in the V territory, branch 1, 2, hyperpigmented conjunctiva + uveal melanoma in white people	– Excision in case of malignant transformation

Table 21.8 Precancerous lesions

Corneal conjunctival intraepithelial neoplasia	– Benign tumors with malignant potential – Risk factors: UV, AIDS infection, papillomavirus – Flat gelatinous tumors, white/pink nipple-like bumps with vascular tuberosities, white leukoplasic or papillomatous lesions with diffuse conjunctival thickening	– Excision and cryotherapy for isolated lesions – For diffuse lesions, excision, topical mitomycin, 5-fluorouracil, interferon
Hereditary intraepithelial dyskeratosis	Rare, bilateral with prominent, gray, intensely vascularized conjunctival plaques	– Clinical follow-up
Melanosis	– 40–50 years old, with corneal invasion + cellular atypia	– Biopsy – Excision, cryotherapy, mitomycin
Actinic keratosis	– Limbic tumor, whitish, vascularized	– Excision
Xeroderma pigmentosum	– After sun exposure, it can degenerate into carcinoma	

Table 21.9 Malignant tumors

Squamous cell carcinoma	– Rare juxtalimbic papillomatous or gelatinous tumor, vascularized with malignant potential (slow) – Can develop after xeroderma or HIV with vegetative tumor	– Excision + cryotherapy for recurrences – Mitomycin, 5-fluorouracil – Chemotherapy – Enucleation, exenteration if needed
Spindle cell carcinoma	– Tumor similar to squamous cell carcinoma, but very aggressive	
Sebaceous gland carcinoma	– Very rarely plaques located on the tarsal conjunctiva	– Excision + cryotherapy – Mitomycin, topical 5-fluorouracil in recurrences
Lymphoma	– Pink/salmon infiltration of the lower sac fundus and globe sometimes bilaterally	– Radiotherapy – Chemotherapy – Excision + cryotherapy
Kaposi sarcoma	– Bright red, flat lesion in the fundus of the inferior sac in AIDS patients	– Radiotherapy – Excision + cryotherapy
Malignant melanoma	– Originates from PAM with atypia (most common) from a preexisting nevus or primitive melanoma (rarest) with onset after the age of 60 – Primitive melanoma (exceptionally in black people) is located on the bulbar conjunctiva as a juxtalimbic black nodule or achromic tumor (fish head appearance) – Melanoma originating from the PAM has the appearance of multiple nodules in the PAM area – 25% mortality in 10 years	– Excision + cryotherapy in circumscribed tumors In diffuse tumor: tumor excision, cryotherapy, mitomycin – Radiotherapy

Table 21.10 Degenerative conjunctival diseases

Pinguecula	– More common in elderly people with slow or absent growth, white/yellowish, round lesion on nasal or temporal limbus in people exposed to the sun	– Corticosteroids in inflammation
Pterygium	– Proliferative, triangular, fibrovascular lesion in the bulbar conjunctiva that may grow into the cornea beyond the limbus – Complications: irritation, astigmatism, decreased VA, Stoecker line (iron deposits on the cornea at the head of the pterygium)	– Simple excision/can be accompanied by recurrences – Mitomycin – Irradiation with beta rays – Excision and grafting

Orbital Tumors: Tables 21.11, 21.12, 21.13, 21.14, 21.15, 21.16, 21.17, 21.18, and 21.19

Benign orbital tumors in children

Dermoid cyst
Hemangioma
Lymphangioma
Neurofibroma
Glioma
Inflammatory pseudotumors

Table 21.11 Benign orbital tumors

Capillary hemangioma	– Present in the first months, increase up to 6–12 months, stabilize, regress in 5–8 years – Variable clinical signs according to location: exophthalmos, ptosis, skin color changes (dark blue) accentuated by crying, effort – Complications: optic nerve compression, necrosis and infection, exposure keratitis	– Treatment in case of complications – Systemic cortisone injection – Resection with an electric scalpel
Cavernous hemangioma	– Affects the young adult, female – Unilateral, non-congestive progressive axial exophthalmos rarely, with optic nerve compression, orbital apex syndrome	– Total excision
Pleomorphic angioma of the lacrimal gland	– 20–50 years old Orbital lobe involvement: slowly progressive tumor with exophthalmos, diplopia, inferonasal dystopia – Damage to the palpebral lobe: swelling of the upper eyelid without dystopia	– Tumor excision with capsule – No biopsy is performed
Fibrous dysplasia of the orbit	– Child, young adult – The most common fibro-osseous tumor in children – Exophthalmia, diplopia due to tumor with progressive evolution	
Eosinophilic granuloma	– Children, teenagers – Rare supero-temporal tumor with painful exophthalmos	– Steroids – Radiotherapy
Lymphangioma	– Child, with damage to the conjunctiva, eyelid, orbit – Rarely, tumor with exophthalmos, slow evolution, progressive or suddenly installed, at superonasal level – Infiltrating tumor	– Monitoring – Could not be operated because it is infiltrative, friable, without a capsule
Fibroma	– Child, adult – Dense, encapsulated tumor in the supero-internal angle with progressive exophthalmos	– Tumor excision
Lipoma	– Tumor located near a nerve or muscle	– Surgical excision

Table 21.12 Cystic orbital tumors

Dermoid cyst	– The most common congenital tumor Cyst anteriorly to the orbital septum—presents supero-temporal subcutaneous nodule Deep cyst, posteriorly to the orbital septum, with exophthalmos, dystopia and requires CT, MRI	– Complete excision with capsule to avoid recurrences
Mucocele	– Cystic accumulation of secretions in the frontal, ethmoid, maxillary sinus (rarely) due to obstruction of sinus drainage – Hard fluctuating formation supero-internally in the orbit	– Surgical exeresis with restoration of drainage from the sinuses
Encephalocele	– Herniation of intracranial contents through a congenital hole at the base of the skull revealed by CT – Different clinical appearance with displacement of the globe and exophthalmos – Can be associated with: hypertelorism, microphthalmia, coloboma, neurofibromatosis	

Table 21.13 Malignant orbital tumors in adults (or with malignant potential)

Optic nerve glioma	– Children—10 years old – Benign tumor in children; in adults, it can be associated with neurofibromatosis type 1 and then it has a malignant character – Tumor with slow evolution with extension to the chiasm, hypothalamus, third ventricle where it is malignant – Clinically: VA decrease, axial exophthalmos, ocular motility disorders, papillary edema, headache due to intracranial extension – CT—fusiform dilatation of the optic nerve MRI shows tumor extension Morbidity and mortality according to tumor extension	– In non-evolving tumor: ophthalmological, neurosurgical surveillance – Tumor excision according to MRI – Do not operate if the tumor is extended in the skull, case in which radiotherapy/chemotherapy is indicated
Optic Nerve Sheath Meningioma (ONSM)	– Very rare at the age of 50–60, unilateral, in women – Metastatic potential Clinically: decreased VA by optic nerve compression, optociliary shunts, ocular motility deficit when looking up, exophthalmos – CT—tubular thickening of the optic nerve MRI—differentiation from glioma (tram track sign)	– Clinical and radiological follow-up because the tumor grows slowly – Surgical exeresis if necessary (to limit the extension to the second optic nerve)
Neurofibroma with two forms	*Plexiform neurofibroma* – 10 years old Clinically—periorbital edema, hypertrophy of the upper eyelid as a "ball of string" with horizontal S-shaped eyelid – Associated with congenital defect of the large wing of the sphenoid	– Surgical treatment is avoided because the tumor is diffuse, without a capsule

(continued)

Table 21.13 (continued)

	Isolated neurofibroma – At the age of 30–40 – Intracapsular tumor, with slow exophthalmos	– Total surgical excision
Glioblastoma	– Adults – Accompanied by complete decrease in VA – Lethal in 3–6 months	
Neurilemmoma (Schwannoma)	– Rare, slowly progressive tumor of peripheral nerves or cranial nerves – Benign tumor, but it can become malignant – Associated with exophthalmos, diplopia, decreased VA	
Malignant lymphoma Lymphosarcoma	– Elderly people with variable, unpredictable evolution – Risk of tumor-related dissemination and death – Progressive exophthalmia – Complex investigations (chest radiology, CT, thoraco-abdominal MRI)	– Radiotherapy for localized lesions – Chemotherapy for disseminated forms
Carcinoma of the lacrimal gland	– At 40–60 years old – Tumor with rapid progression (death in 6 months) – Reserved prognosis – Biopsy for the therapeutic attitude Clinically—lacrimal gland hypertrophy with inferonasal dystopia, hypoesthesia (lacrimal nerve), periorbital edema, ophthalmoplegia – Neurological examination for possible invasion of the cavernous sinus	– Tumor removal (rarely possible) – Radiotherapy associated with total resection
Osteosarcoma	– Reserved prognosis – Traumatic antecedents or after 10–30 years after retinoblastoma relapsed	
Ewing sarcoma	– At 20–30 years old – Osseous origin in axial skeleton, long bones Metastatic orbital tumor with exophthalmos, hemorrhages and inflammation, tumor necrosis	– Radiosensitive – Fatal evolution

Table 21.14 Malignant tumors in children

Rhabdomyosarcoma	– Most common primary malignant tumor in children, boys (10 years old) – Possible hematogenous, lymphatic dissemination – Rapidly progressive exophthalmos, ptosis, redness of the skin of the eyelids without burning sensation, which may mimic an inflammatory process – Located in the muscle cone, CT, MRI reveals the tumor and bone lysis – General clinical examination	– Radiotherapy – Chemotherapy – Surgical exeresis for the tumor resistant to radiotherapy
Plexiform neurofibroma		
Granulocytic sarcoma (chloroma)	– Localized tumor composed of malignant cells of myeloid origin – 10 years – Rapidly progressive exophthalmia, sometimes bilateral, purple eyelid	

Table 21.15 Metastatic tumors in children

Neuroblastoma	– The most common metastatic tumor in children – Before the age of 5 – The primary tumor is in the abdominal, thoracic, pelvic sympathetic ganglion chain – 15% survival rate – Fast-growing superolateral orbital tumor (sometimes bilateral) with exophthalmia, edema and palpebral ecchymosis	– Incisional biopsy – Radiotherapy – Chemotherapy
Ewing sarcoma		
Langerhans cell histiocytosis	– Childhood onset with bone and soft tissue lesions – Exophthalmia with superotemporal localized tumor	

Table 21.16 Inflammatory pseudotumors

– Women of 20–40 years old – Sometimes bilateral – Orbital tumor with exophthalmos, limitation of motility – Histological examination—chronic, non-specific inflammation	– Systemic corticosteroids – Cytotoxic agents

Table 21.17 Benign tumors spread to the orbit

Meningioma of lesser wing of sphenoid	– Reduced exophthalmos, but tumor growth in the orbit simulates a primary tumor
Nasopharyngeal fibroma	– Adolescents, males – Large exophthalmos with palpebral edema, oculo-motor paralysis, blindness

Table 21.18 Intraocular tumors spread to the orbit

Neglected retinal glioma	Monstrous tumor
Melanic sarcoma of the choroid	– It can spread in the orbit with relapses years after enucleation

Table 21.19 Soft tissue tumors spread to the orbit

Palpebral epithelioma	
Conjunctival neocarcinoma	– When the tumor is on the caruncle, semilunar fold – Infiltrative nodular orbital tumor with pigmentation spots
Mucocele	

Metastatic Tumors in the Orbit: Tables 21.20, 21.21, and 21.22

Table 21.20 Tumors of the cornea

Men	Lung, prostate, gastrointestinal neoplasm
Women	– Breast, lungs neoplasm

Table 21.21 Benign tumors

Fibroma	– Dermoid appearance, but the corneal epithelium is intact

Table 21.22 Malignant tumors

Primitive carcinoma	– Corneo-conjunctival epithelial neoplasia more common in elderly men or young people with xeroderma, immunosuppression – Appears on normal cornea or with a post-pterygium scar, ulcer, has a varied clinical appearance, slow evolution, in depth and towards the conjunctiva, and is minimally invasive, but relapses after surgery are frequent	– Exeresis with recurrence good prognosis – Radiotherapy
Melanoma	– Very rarely, it is radiosensitive in very high, incompatible doses	– Exeresis
Intraepithelial carcinoma—Bowen	– Precancerous dermatosis is a slightly elevated, vascularized, poorly demarcated tumor with gelatinous appearance, is present in elderly (men) with questionable invasion	– Surgical excision – Lamellar keratotomy

Tumors of the Limbus: Tables 21.23 and 21.24

Table 21.23 Benign tumors

Limbic dermoid (congenital)	– Can be accompanied by: uveal coloboma, eyelid, facial malformations, encephalocele	– Excision
– Inclusion cyst	– It can develop after a limbal wound in the form of a bosselated tumor on the limbus	
– Papilloma	– Sessile or pedunculated, single or multiple muriform	– Extirpation when needed, but with relapses
– Neurinoma	– În neurofibromatosis	
– Lymphoma	– In leukemia, tumors of the limbus	
– Tumors in patients with xeroderma	– They have a familial character, develop in the first 10 years, with limbic tumors of variable sizes	

Table 21.24 Malignant tumors

Carcinoma of the limbus	– More commonly squamous cell; is a tumor implanted on a surface with vascular bundles, with a tendency to invade the sclera, cornea, Tenon's capsule, with slow evolution (years), but can be lethal as a result of metastases	
– Melanoma tumor two forms	– Carcinoma developed on pre-existing limbal nevus Limbic nevocytoma—extremely malignant tumor with a dismal prognosis	– Enucleation – Exenteration – Radiotherapy

Scleral Tumors: Tables 21.25 and 21.26

Table 21.25 Episcleral tumors

Osseous chorystoma	– Congenital temporal superior tumor 5–10 mm from the limbus, adherent to the sclera, containing bone
Fibroxanthoma (histiocytoma)	– Frequent localization in the orbit, but can also occur in the episclera, with local invasion
Reticulohistiocytoma	
Xanthoma disseminatum	– Affects the skin, throat, eyelids, tongue, superior sclero-cornea, axilla, antecubital fossa, perianal region, inguinal fold, pharyngeal oral mucosa with yellow/orange small papules
Melanocytoma	– Very rare tumor; it can extend to the orbit

Table 21.26 Tumors of the sclera

Fibroma	– May be scleral, episcleral
Fibrosarcoma	– After recurrent scleritis, with adjacent malignant invasion, but few metastases
Nodular fasciitis	– Rapid pseudotumoral proliferation at the level of the eyelids, sclera, fascia, conjunctival septum, but also the head and neck skin, with healing after excision
Hemangioma	– Very rarely, in Sturge-Weber syndrome
Neurofibroma	– Isolated or in neurofibromatosis
Scleral cyst	– Congenital or posttraumatic
Dermoid cyst	– Located inferotemporally near the limbus, it may be associated with systemic diseases (Goldenhar syndrome) – Excision when it is unaesthetic, they cause VA decrease, leading to high astigmatism
Osseous chorystoma: osteoma, chondroma	– They can contain cartilage, bone, adhering to the sclera

Secondary Tumors

Through the scleral invasion of the neighboring tumor: orbit, conjunctiva, eyelids, uvea, retina.

Tumors of the Iris: Tables 21.27, 21.28, 21.29, and 21.30

Table 21.27 Iris malignant tumors

Primary iris cysts	• *Epithelial cyst* present in adults, single, unilateral, located on the edge of the pupil, at the root of the iris or between them; is a round brownish lesion, can be posttraumatic, pearly, congenital, iatrogenic (after miotics) • *Stromal cyst* – Present in the first year, with a single, unilateral lesion, with a translucent anterior wall, containing fluid – Can be complicated with secondary glaucoma	Aspiration – Surgical excision
Iris nevus	– Typical—pigmented, flat, or slightly raised lesion that can cause iris ectropion and sectorial cataract – Diffuse—can be associated with Cogan-Reese syndrome – Rarely can degenerate in MM	**– Iridectomy if needed**
Leiomyoma	– Women, 30–50 years old, inferior temporal – In evolution it can be complicated with intraocular hypertension, cataract, hyphema, ciliary body invasion	
Nevoxanthoma-endothelioma	– Child under 6 months old with recurrent spontaneous hyphema and evolution towards secondary glaucoma with buphthalmia	– Corticoids – Radiotherapy – Iridectomy
Angioma	– Very rarely in angiomatosis	

Table 21.28 Malignant tumors

Iris melanoma	– Accounts for 5% of uveal melanomas and is a rare pigmented (or not) iris nodule with vessels on the surface, more often located in the lower half of the iris, with pupillary deformity, uveal ectropion and cataract – Predisposition to uveal melanomas are given by: congenital ocular melanocytosis, dysplastic cutaneous nevus, familial cutaneous melanoma, neurofibromatosis	– Small tumor—iridectomy – Tumor with angle invasion – Iridocyclectomy – Large tumors—external radiotherapy, brachytherapy Enucleation—extended tumors

Table 21.29 Metastatic tumors

– There can be multiple uveal locations
– They are uni-, bilateral, by blood dissemination

Table 21.30 Secondary iris tumors

– From conjunctival, corneal tumor, exceptionally orbital

Ciliary Body Tumors: Tables 21.31, 21.32, and 21.33

Table 21.31 Congenital benign tumors

Medulloepithelioma (dictyoma)	– 4–12 years old, benign or malignant tumor that can block the angle, with rare metastases even if it degenerates malignantly	– Iridocyclectomy for small tumors – Enucleation for large tumors
Adenoma	– Located in pigmented, rarely unpigmented ciliary epithelium; it is difficult to differentiate from ciliary body malignant melanoma (MM)	
Hyperplasia of ciliary body	– Post-traumatic, post-inflammatory, can grow and simulate a melanoma	

Table 21.32 Acquired benign tumors

Nevi	– They can be discovered on eyes enucleated from other causes
Hemangioma	– Clinically invisible
Leiomyoma	– Very rarely
– Pseudoadenomatous hyperplasia	– Rarely it is clinically apparent as an irregular bright white tumor

Table 21.33 Malignant tumors of the ciliary body

Ciliary body melanoma	– It represents 10% of uveal melanomas – After the age of 60, the barely visible tumor requires mydriasis, gonioscopy, careful examination for diagnosis – At the periphery of the eye fundus, the dark brown elevated nodular tumor with dilated episcleral vessels, "sentinel vessels" in the quadrant where the tumor is, with extraocular extension, as a black epibulbar mass, or after iris erosion, extension in the anterior chamber	– Treatment depends on: enlargement, localization and extension of the tumor, VA, uni/bilateral character, age, general clinical condition
	– Some necrotic forms can cause inflammatory symptoms in uveitis – Other forms of tumor can grow circularly – Annular melanoma (reserved prognosis) – Complications—lens subluxation, cataract, secondary glaucoma, RD, choroidal neovascularisation (CNV) – The treatment depends on: the size, location and extension of the tumor, VA	
Diktyoma	– Malignant tumor with primary embryonic structure or by degeneration of the benign tumor	
Adenocarcinoma		
Cystic adenoma		
Leiomyoma		

Metastatic Tumors

It mostly affects the choroid, exceptionally the iris, ciliary body.

Choroid Tumors: Tables 21.34, 21.35, 21.36, and 21.37

Table 21.34 Benign tumors

Choroidal hemangioma	• Two forms – Diffuse in Sturge-Weber syndrome on the same side as the nevus – Circumscribed—round (oval), red-orange, centrally located tumor • Both can be complicated with retinal degeneration, exudative RD	– Photocoagulation – Radiotherapy – Cryotherapy – Enucleation of the eye without VA
Cavernous hemangioma	– Isolated or associated with nevus flammens and glaucoma in Sturge-Weber syndrome	– Photocoagulation
Nevi	– Slate blue or gray-green lesion with drusen on the surface (they can also be hypopigmented nevi, but have a hyperpigmented ring) showing the chronic evolutionary character	– Typical nevus should not be followed-up – Suspected nevus should be followed-up every 6 months for years
	– Angiofluorography (AFG)—tumor masking and drusen hyperfluorescence – A nevus that presents symptoms, is larger than 5 mm in diameter and 1 mm in thickness, with lipofuscin on the surface (orange pigment) is located close to the papilla (below 3 mm), lacks drusen, has serous RD should be suspected	
Neurofibroma leiomyoma	– Rarely	
Lymphoma	– It can be accompanied by anterior, intermediate, posterior uveitis	– Radiotherapy – Chemotherapy
Osteoma	– Present in young women, bilateral (25%), is frequently asymptomatic, has a slow evolution, can be complicated with CNV – Reserved prognosis	– Laser photocoagulation
Melanocytoma	– Present in melanodermic patients, discovered by highlighting black, poorly circumscribed papillary lesions—AFG shows dilated superficial capillaries and masking of the large deep vessels	– Treatment is only necessary in case of malignant transformation

Table 21.35 Malignant tumors

Choroidal melanoma	– It represents 85% of uveal melanomas and is the primary intraocular tumor, the most common in adults – Onset at the age of 60 (23–85 years) with a prominent subretinal tumor, brownish, with orange pigment on the surface (lipofuscin)—**sign for the malignant nature of the lesion,** with different metastasizing capacity according to size, vascularization—**with double network choroidal and tumoral vascularity**, pigmentation, absence of drusen	– **Periodic observation** for small tumors with slow evolution in patients over 65 years old – **Conservative treatment** with iridectomy, sectorial cyclochoroidectomy – **Brachytherapy** in tumors less than 10 mm in thickness and 20 mm in diameter – **External radiotherapy** in tumors incompatible with brachytherapy and located near the papilla and fovea – Complications: madarosis, epiphora, conjunctival keratinization, keratitis, exudative RD, glaucoma
	The tumor can be accompanied by tumor RD, cataract + lens subluxation, uveitis, vitreous hemorrhages – Ultrasound shows a homogeneous lesion with low or medium reflectivity, with choroidal excavation and orbital shadow cone Early AFG shows double circulation, and late-diffusion and a progressive staining – **The correct positive diagnosis made quickly can reduce the number of enucleated eyes** – Variable evolution with: tumor necrosis that can lead to uveal inflammation, ocular hypertonia, extension in the orbit, blood metastases in the liver, lung CNS, relapses after enucleation – Uveal melanomas (Callender) can be AB spindle cell 45%, epithelioid cell 5%, spindle and epithelioid cell 45%, and necrotic 5% – Reserved prognostic factors are: the presence of epithelioid cells, closed vascular loops at the level of the tumor, lymphocytic infiltration, but also large tumors, extrascleral extension, previous localization, age over 65, chromosomal abnormalities – The differential diagnosis is made with other choroidal tumors (giant nevus, metastases, circumscribed hemangioma), unique choroidal granuloma in TB; sarcoidosis or posterior scleritis – A general medical examination is necessary for the research of choroidal metastases in bronchial, breast, kidney, digestive tract cancer and liver metastases	Neovascular – **Trans-pupillary thermotherapy** in small tumors, near the papilla, fovea – **Local exeresis** in thick tumors that cannot receive radiotherapy – **Stereotactic radiosurgery** with protons, alternative therapy to external radiotherapy – **Enucleation** in large tumors with low VA – **Exenteration** in tumor extension or recurrences after enucleation – **Chemotherapy** in case of metastases

(continued)

Table 21.35 (continued)

Lymphoma	– It develops in the brain, spinal cord, meninges + eyes and has a reserved prognosis	– Radiotherapy – Chemotherapy – Intravitreal methotrexate
B-cell non-Hodgkin's lymphoma	– The diagnosis is made by the presence of chronic anterior uveitis that does not respond to corticosteroids, intermediate uveitis with major vitreous disorder or posterior uveitis with multiple yellowish infiltrates under pigment epithelium – Difficult diagnosis, early diagnosis does not decrease mortality, but increases survival rate – In HIV patients, it is very aggressive	– External radiotherapy – Chemotherapy – Methotrexate

Table 21.36 Intraocular tumor simulators

Uveal effusion syndrome	– Present in middle age, males with exudative RD (B-cell non-Hodgkin lymphoma must be ruled out), syphilis, posterior scleritis, TB, nanophthalmia, sarcoidosis – Piles of retinal pigment, thick sclera	– Corticotherapy—less effective – Scleral resection (possible)
Nanophthalmia	– Normal eyes but smaller anteroposterior diameter, choroidal folds, thicker sclera, decreased uveo-scleral flow – Ultrasound diagnosis	
Vogt-Koyanagi-Harada syndrome		

Table 21.37 Choroidal metastases

– Rapidly growing creamy-white lesions or multiple, bilateral deposits associated with serous RD	– Surveillance radiotherapy – Enucleation of painful eye

Tumors of the Retina and Optic Nerve: Tables 21.38 and 21.39

Table 21.38 Congenital tumors of the retina and RPE

Retinal capillary hemangioma	– Onset at 20–30 years old with decreased VA and visual field; it may be associated with von Hippel–Lindau disease – A single, multiple, peripherally located red-orange nodule is present with dilations and tortuosity of the arteries and veins, with exudates that can surround the tumor, sometimes hemorrhages that start from the tumor	– Argon laser photocoagulation for peripheral lesions – Cryotherapy for large lesions associated with RD – Brachytherapy
Retinal cavernous hemangioma	– Retinal lesion, rarely progressive, unilateral, is accompanied by vascular lesions in the CNS, skin, with onset at 20–30 years of age; it manifests as dark red saccular aneurysms, resembling "bunches of grapes", without exudates	– Treatment is only necessary in complications such as vitreous hemorrhage
Retinal racemose hemangioma	– It is a congenital, unilateral arterio-venous malformation, discovered by chance, with numerous wide tortuous vessels that can occupy the entire eye fundus – May extend to the mandible, orbit and may be associated with intracranial lesions in Wyburn-Mason syndrome	
Congenital hypertrophy of pigment epithelium with two forms	– Optical form with single, well-demarcated, dark gray or black lesion or clustered black lesions ("bear tracks" pigmentation) Atypical form with oval, fusiform, bilateral, multiple lesions, with hypopigmented edges Systemic approaches with: familial adenomatous polyposis—FAP (AD associated with colorectal carcinoma), Gardner syndrome with FAP, osteoma, skin tumor, Turcot syndrome with FAP, CNS tumors	
Combined hamartoma of the retina and retinal pigment epithelium	• Present in neurofibromatosis-2, with localization: – Juxtapapillary—with VA decrease in young adults and gray, brown, slightly raised lesions associated with epiretinal gliosis and dilated and tortuous capillaries – Peripheral—present in children with strabismus, with linear lesions associated with vascular deformations – Complications: retinal and papillary distortion, macular edema, CNV, RD – Vitrectomy if needed	
Hamartoma of retinal pigment epithelium	– Small black spots, sometimes macular with extension in the surface of the retina	

Table 21.39 Retinal malignant tumors

Retinoblastoma Retinoblastoma is the most common primary intraocular malignancy in childhood, with stopped evolution, with hereditary form, AD, with a 50% risk of transmission, of which 50% of the offspring may develop RB and non-hereditary sporadic forma in 60% of cases, 85% unilateral RB with non-transmissible tumor. The major clinical signs are: leukoria (white reflex in the pupil amaurotic cat's eye), strabismus, painfully red eye, associated with orbital inflammation Tscan, MRI high lighting calcifications, optic nerve invasion. CNS extension, CNS extension presence of pineablastoma, Bscan RB can be complicated by: cataract, secondary glaucoma, retinal detachment, vitreous, hemorrhagic. Prognosis of the disease is relatively good, with 70–85% survival rate, if enucleation was done before the extraocular extension of the tumor treatment. Reserved prognostic: large tumor, with reduced cellular differentiation, optic nerve invasions. Reserved vital prognosis for the forme with extrascleral extension. Treatment in RB depends on the size and location of the tumor	**Treatment** • Long section enucleation of optic nerve (more than 5 mm) – External radiotherapy – Brachytherapy – Chemotherapy Locally: – Cryotherapy – Xenon photocoagulation – Iodine-125 brachytherapy – Thermochemotherapy (carboplatin followed by diode laser) • Treatment depending on tumor size – Small tumors—cryotherapy – Medium tumors—brachi-, cryotherapy – Large and extensive tumors, enucleation – Enucleation is indicated in large tumors, extensive RD, in optic nerve invasion secondary glaucoma • Chemotherapy in metastatic tumors • Treatment for optic nerve invasion – Radiotherapy – Chemotherapy • Palliative treatment – Chemotherapy – Exenteration
Pseudo retinoblastoma	– There are lesions that can simulate RB: astrocytic hamartoma, Coats disease, etinal capillary hemangioma
Retinocytoma	– Benign tumor with genetic transmission, clinical appearance similar to RB, but is present in older children, young adults
Astrocytoma	– Bilateral 15%, present in 50% of people with tuberous sclerosis

Metastatic Tumors (Table 21.40)

They are hematogenous disseminations in men—lung cancer, skin melanoma; in women—breast, lung, gastrointestinal cancer.

Table 21.40 Phakomatoses

Von Hippel—Lindau – cerebroretinal angiomatosis	– AD familial disease, chromosome 3p25 characterized by the presence of ocular, brain (cerebellum), renal, adrenal hamartomas – Retinal angioma is a round, red-orange retinal tumor with a tortuous draining artery and vein – Complications: RD, macular edema
Sturge-Weber encephalotrigeminal angiomatosis	– Angioma on the Vth CN pathway – Complicated diffuse choroidal angioma with exudative RD, vitreous hemorrhages, secondary glaucoma – Laser photocoagulation – External radiotherapy
Neurofibromatosis 1—Von Recklinghausen	– CNS hamartoma, skin, eye – Multisystem disease, AD, chromosome 17q with cutaneous neurofibromas, cerebral meningiomas and gliomas, retinal astrocytomas, Lisch iris nodules, renal carcinomas, pheochromocytoma
Neurofibromatosis 2	– AD, chromosome 22 – Clinically: bilateral (uni-) acoustic neuroma, meningioma, Schwannoma, glioma, cerebellopontine angle tumors
Bourneville tuberous sclerosis	– It manifests as retinal astrocytoma with epilepsy, sebaceous adenoma, mental retardation – Chromosome 9, 16
Wyburn–Mason racemose hemangiomatosis	– Unilateral, non-hereditary condition with retinal racemose hemangioma possibly complicating with vitreous hemorrhages and glaucoma – There can be arterio-venous malformations in the brain with convulsive seizures, mental changes

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